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PROCEEDINGS

OF THE

PATHOLOGICAL SOCIETY

OF PHILADELPHIA.

NEW SERIES, VOLUME VII.
OLD SERIES, VOLUME XXV.

CONTAINING THE TRANSACTIONS OF THE SOCIETY FROM DECEMBER, 1903, TO NOVEMBER, 1904.

EDITED BY

DAVID RIESMAN, M.D.,
RECORDER OF THE SOCIETY.

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PHILADELPHIA:
PRINTED FOR THE SOCIETY BY WM. J. DORNAN.
1904.

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FORMER PRESIDENTS.

SAMUEL D. GROSS, M.D., LL.D., D.C.L. OXON., LL.D. CANTAB., elected 1857.

RENÉ LA ROCHE, M.D., elected 1858.

ALFRED STILLÉ, M.D., LL.D., elected 1859, '61, and '62.

EDWARD HARTSHORNE, M.D., elected 1860 and '63.

J. M. DA COSTA, M.D., LL.D., elected 1864, '65, and '66.

JOHN H. PACKARD, M.D., elected 1867 and '68.

S. WEIR MITCHELL, M.D., LL.D., elected 1869.

JOHN ASHHURST, JR., M.D., LL.D., elected 1870.

JAMES H. HUTCHINSON, M.D., elected 1871 and '72.

WILLIAM PEPPER, M.D., LL.D., elected 1873.

H. LENOX HODGE, M.D., elected 1876.

S. W. GROSS, M.D., elected 1879.

JAMES TYSON, M.D., elected 1882 and '83.

E. O. SHAKESPEARE, M.D., elected 1884.

J. C. WILSON, M.D., elected 1885 and '86.

F. P. HENRY, M.D., elected 1887 and '88.

HENRY F. FORMAD, M.D., elected 1889 and '90.

ARTHUR V. MEIGS, M.D., elected 1891 and '92.

J. H. MUSSER, M.D., elected 1893, '94, '95, and '96.

W. E. HUGHES, M.D., elected 1897 and '98.

F. A. PACKARD, M.D., elected 1899 and 1900.

CHARLES W. BURR, elected 1901 and 1902.

OFFICERS AND COMMITTEES

OF THE

PATHOLOGICAL SOCIETY OF PHILADELPHIA.

(List of officers elected October 8, 1903.)

President.

ALFRED STENGEL, M.D.

Vice-Presidents.

JOSEPH McFARLAND, M.D.,
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J. SAILER, M.D.,
W. M. L. COPLIN, M.D.

Secretary.

D. J. McCARTHY, M.D.

Recorder.

DAVID RIESMAN, M.D.

Treasurer.

THOMPSON S. WESTCOTT, M.D.

Curator.

A. P. FRANCINE, M.D.

Membership Committee.

WM. PEPPER, M.D.,
GEORGE P. MULLER, M.D.,
G. M. COATES, M.D.

Committee on Morbid Growths.

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J. D. STEELE, M.D.

Publication Committee.

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JOSEPH McFARLAND, M.D.

Business Committee.

C. W. BURR, M.D.,
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A. O. J. KELLY, M.D.,
J. D. STEELE, M.D.

OFFICERS AND COMMITTEES

OF THE

PATHOLOGICAL SOCIETY OF PHILADELPHIA.

(List of officers elected October 13, 1904.)

President.

ALFRED STENGEL, M.D.

Vice-Presidents.

JOSEPH McFARLAND, M.D., A. J. SMITH, M.D.,
M. P. RAVENEL, M.D., W. M. L. COPLIN, M.D.

Secretary.

D. J. McCARTHY, M.D.

Treasurer.

THOMPSON S. WESTCOTT, M.D.

Recorder.

D. L. EDSALL, M.D.

Curator.

A. P. FRANCINE, M.D.

Business Committee.

C. W. BURR, M.D., DAVID RIESMAN, M.D.,
D. L. EDSALL, M.D., A. O. J. KELLY, M.D.,
J. D. STEELE, M.D.

Membership Committee.

WM. PEPPER, M.D., GUTHRIE McCONNELL, M.D.,
JOSEPH C. ELLIS, M.D.

Publication Committee.

DAVID RIESMAN, M.D., A. O. J. KELLY, M.D.,
JOSEPH McFARLAND, M.D.

Committee on Morbid Growths.

W. E. ROBERTSON, M.D., GEORGE P. MULLER, M.D.,
J. D. STEELE, M.D.

LIST OF MEMBERS.

ORIGINAL MEMBERS.

JOHN H. BRINTON, 1423 Spruce Street.
JAMES DARRACH, 5923 Greene Street, Germantown.
S. WEIR MITCHELL, 1524 Walnut Street.
GEORGE R. MOREHOUSE, 2033 Walnut Street.
JOHN H. PACKARD, Hotel Stenton.

MEMBERS.

ELECTED

1894 Abbott, A. C., 4229 Baltimore Avenue.
1899 Adler, L. H., Jr., 1610 Arch Street.
1904 Alburger, H. R., The Covington.
1903 Allen, F. O., Pennsylvania Hospital.
1898 Allen, W. L., 3100 Wharton Street.
1889 Anders, J. M., 1605 Walnut Street.
1901 Anspach, B. M., 4824 Baltimore Avenue.
1900 Artelt, H., 1521 North Eighth Street.
1891 Ashton, Thomas G., 1814 South Rittenhouse Square.
1895 Ashton, William E., 2011 Walnut Street.

1897 Babcock, W. Wayne, 3302 N. Broad Street.
1898 Baggs, Albert N., P. O. Box, 102, Abington, Pa.
1887 Baker, G. F., 1818 Spruce Street.
1888 Balliet, Tilghman M., 3705 Powelton Avenue.
1898 Bardsley, G., 2111 North Howard Street.
1885 Beates, Henry, Jr., 1504 Walnut Street.
1900 Behrend, Moses, 1331 North Franklin Street.
1871 Bennett, Wm. H., 2105 Spruce Street.
1887 Berens, Bernard, 2041 Chestnut Street.
1900 Bergey, D. H., 521 N. Thirty-fifth Street.
1894 Beyea, H. D., 1411 Spruce Street.
1904 Biddle, Clement, League Island Navy Yard.
1901 Biggs, M. H., Philadelphia Hospital.

ELECTED
1892 Birney, D. B., 1810 De Lancey Place.
1893 Bochroch, Max H., 937 North Eighth Street.
1886 Bodamer, George A., 1507 Girard Avenue.
1892 Boger, John A., 2213 North Broad Street.
1898 Boston, L. Napoleon, 1531 South Broad Street.
1893 Boyer, H. P., 4602 Baltimore Avenue.
1857 Brinton, John H., 1423 Spruce Street.
1898 Brinton, Ward, 1423 Spruce Street.
1896 Brown, H. MacV., 4608 Baltimore Avenue.
1904 Brown, H. M., 4608 Baltimore Avenue.
1895 Brubaker, A. P., 105 North Thirty-fourth Street.
1893 Bryan, J. Roberts, 4200 Chestnut Street.
1901 Buckley, A. C., 1705 North Fifteenth Street.
1887 Burr, Charles W., 1327 Spruce Street.

1902 Carncross, H. L., 721 Pine Street.
1903 Carnett, J. B., 247 South Thirteenth Street.
1893 Carpenter, H. B., 1805 Spruce Street.
1902 Carpenter, H. C., 1805 Spruce Street.
1897 Carpenter, J. T., Jr., 1624 Walnut Street.
1887 Cattell, H. W., 3709 Spruce Street.
1898 Chestnut, J. E., 1817 Frankford Avenue.
1887 Chrystie, Walter, Bryn Mawr, Pennsylvania.
1899 Clark, John G., 218 South Fifteenth Street.
1866 Cleemann, Richard A., 2135 Spruce Street.
1898 Coates, George M., 334 South Nineteenth Street.
1901 Coca, A. F., Medical Department, University of Pennsylvania.
1900 Codman, C. A. E., 328 South Forty-second Street.
1872 Cohen, J. Solis, 1824 Chestnut Street.
1902 Cohen, M. Solis., Forty-first Street and Parkside Avenue.
1883 Cohen, S. Solis, 1525 Walnut Street.
1896 Coley, Thomas Luther, 257 South Twenty-first Street.
1890 Coplin, M. M. L., 1629 South Broad Street.
1901 Craig, F. A., 237 South Thirteenth Street.
1903 Crampton, G. S., 1013 Spruce Street.
1899 Cruice, John M., 114 North Eighteenth Street.
1901 Cryer, M. H., 1420 Chestnut Street.
1904 Cummings, W. T., Medical Department, University of Pennsylvania.
1898 Currie, Thos. R., 113 East Cumberland Street.
1871 Curtin, Roland G., 22 South Eighteenth Street.

1894 Da Costa, J. Chalmers, 2045 Walnut Street.

ELECTED

1896 Da Costa, J. C., Jr., 1022 Spruce Street.
1885 Daland, Judson, 317 South Eighteenth Street.
1902 Dare, A. E., 1900 Chestnut Street.
1857 Darrach, James, 5923 Greene Street, Germantown (O. M.).
1900 Darrah, P. W., 3439 Woodland Avenue.
1882 Davis, G. G., 255 South Sixteenth Street.
1893 Davisson, Alexander H., 2024 Pine Street.
1900 Deal, J. C., 5301 Haverford Avenue.
1889 Deaver, H. C., 1534 North Fifteenth Street.
1885 Deaver, J. B., 1634 Walnut Street.
1882 Dercum, F. X., 1719 Walnut Street.
1904 Dever, Francis T., 5050 Cedar Avenue.
1902 Dorrance, G. M., 328 South Seventeenth Street.
1901 Dorsett, R. S., 1105 North Fortieth Street.
1894 Dougherty, S. W., 256 South Sixteenth Street.
1889 Downs, Norton, 215 West Walnut Lane, Germantown.
1903 Drein, W. C., Fifteenth and Jefferson Streets.
1866 Duer, Edward L., 1606 Locust Street.
1876 Dulles, C. W., 4101 Walnut Street.
1883 Dunmire, G. B., 1618 Spruce Street.
1860 Dunton, W. R., High Street and Germantown Avenue, Germantown.
1900 Dye, F. H., 1216 Brown Street.

1896 Edsall, David L., 1432 Pine Street.
1902 Ellis, A. G., 2524 North Seventeenth Street.
1900 Elmer, W. G., 3904 Locust Street.
1900 Erck, T. A., 338 South Thirteenth Street.
1891 Eshner, A. A., 1019 Spruce Street.
1902 Evans, J., 247 South Thirteenth Street.

1901 Farr, C. B., 326 South Seventeenth Street.
1892 Fenn, William B., Denver, Col.
1881 Fenton, T. H., 1319 Spruce Street.
1903 Fife, C. A., 1432 Pine Street.
1876 Fisher, Henry M., 317 South Twelfth Street.
1903 Fox, H., 4443 Spruce Street.
1894 Fox, L. Webster, 1304 Walnut Street.
1899 Francine, A. P., 1404 Spruce Street.
1895 Frazier, Charles Harrison, 133 South Eighteenth Street.
1894 French, Samuel, Plymouth, Pa.
1889 Frese, Carl, 1338 Walnut Street.
1890 Friebis, George, 1906 Chestnut Street.

ELECTED
1903 Funcke, J., 1130 Spruce Street.
1885 Fussell, M. H., 189 Green Lane, Manayunk.

1902 Geisler, Howard D., 202 High Street, Germantown.
1897 Gerson, T. P., Lansdowne.
1870 Getchell, Frank H., 1432 Spruce Street.
1902 Gildersleeve, Nathaniel, Laboratory of Hygiene, University of Pennsylvania.
1902 Gilliland, S. H., University Dormitories.
1900 Gilpin, S. F., Fifty-fifth Street and Girard Avenue.
1894 Girvin, John H., 3924 Walnut Street.
1902 Githens, T. S., 1337 Pine Street.
1898 Gittings, J. Claxton, 3942 Chestnut Street.
1899 Given, E. E. W., 2714 Columbia Avenue.
1882 Godey, H. E., N. E. corner Nineteenth and Spruce Streets.
1900 Goepp, R. M., 1713 Pine Street.
1895 Goritee, C. J., 1117 Spruce Street.
1902 Graham, E. E., 1713 Spruce Street.
1890 Grayson, C. P., 251 South Sixteenth Street.
1867 Grier, Mathew J., 1531 Spruce Street.
1883 Griffith, J. P. C., 1810 Spruce Street.
1897 Gross, Wm., 701 North Fortieth Street.
1890 Gummey, Frank B., 5418 Greene Street, Germantown.
1900 Gwyn, N. B., 23 South Twenty-first Street.

1893 Hamill, S. M., 1822 Spruce Street.
1893 Hand, Alfred, Jr., 1724 Pine Street.
1885 Hare, Hobart Amory, N. W. cor. Eighteenth and Spruce Streets.
1857 Harlan, G. C., 1515 Walnut Street (O. M.).
1902 Harland, W. G., 126 South Nineteenth Street.
1890 Hartzell, M. B., 3644 Chestnut Street.
1904 Hatfield, C. J., 256 South Eighteenth Street.
1901 Hawke, W. W., Philadelphia Hospital.
1900 Head, J., 1500 Locust Street.
1873 Hearn, W. Joseph, 1120 Walnut Street.
1870 Henry, Frederick P., 1635 Locust Street.
1896 Henry, John M., 219 South Seventeenth Street.
1903 Herzberg, M., 512 North Sixth Street.
1880 Hewson, Addinell, Jr., 1115 Spruce Street.
1901 Hickman, W. A., 612 Pacific Avenue, Atlantic City.
1903 Hill, H. K., 1916 Spruce Street.
1899 Hitchens, A. P., Glenolden, Pennsylvania.
1902 Hodge, E. D., 346 South Fifteenth Street.

ELECTED

1899 Holloway, T. B., 49 North Fifty-second Street.
1904 Hoyt, D. M., 3604 Chestnut Street.
1894 Hughes, George M., 241 North Eighteenth Street.
1882 Hughes, W. E., 3726 Baring Street.
1904 Hume, J. E., 900 South Forty-ninth Street.
1901 Hunsicker, C. H., 1614 North Broad Street.
1902 Hunter, John W., 1172 South Broad Street.

1901 Irwin, J. W., 1918 Vine Street.

1890 Jarrett, Henry, Broadway and Cherry Streets, Camden, N. J.
1904 Jenks, Horace H., 920 Clinton Street.
1895 Jopson, J. H., 334 South Sixteenth Street.
1898 Judson, Chas. F., 1539 Pine Street.
1899 Jump, H. D., 4634 Chester Avenue.
1885 Jurist, L., 916 North Broad Street.

1898 Kalteyer, F. J., 1702 Pine Street.
1901 Kane, J. A. B., 211 South Seventeenth Street.
1895 Kelly, A. O. J., 1911 Pine Street.
1899 Kennedy, L. F., 301 Mauch Chunk Street, Pottsville, Pa.
1904 Kiefer, Charles, 1723 North Forty-second Street.
1902 Kinyoun, J. J., Glenolden, Pennsylvania.
1888 Kirby, Ellwood R., 1202 Spruce Street.
1900 Kirk, E. C., Dental Hall, University of Pennsylvania.
1900 Klapp, W. P., 1716 Spruce Street.
1890 Kneass, Samuel S., The Warwick, Nineteenth and Sansom Streets.
1898 Knipe, J. C., S. E. corner Fifteenth and Diamond Streets.
1901 Kohn, B., 1325 North Thirteenth Street.
1895 Krusen, Wilmer, 127 North Twentieth Street.
1892 Kyle, D. Braden, 1517 Walnut Street.

1899 Landis, H. R. M., 225 South Twentieth Street.
1890 Laplace, Ernest, 1828 South Rittenhouse Square.
1898 Latta, Samuel W., 3626 Baring Street.
1894 Leach, W., Eastern State Penitentiary, Medical Department.
1869 Leaman, Henry, 828 North Broad Street.
1903 Lee, W. E., 823 North Twenty-fourth Street.
1888 Leidy, Joseph, 1319 Locust Street.
1887 Leopold, Isaac, 1520 Franklin Street.
1904 Leopold, S., 1632 Franklin Street.
1902 Levi, I. V., 1733 North Sixteenth Street.
1875 Lewis, Morris J., 1316 Locust Street.

ELECTED
1894 Lincoln, C. W., 5348 Wayne Avenue, Germantown.
1899 Lindauer, Eugene, 2018 North Thirty-second Street.
1886 Lloyd, James Hendrie, 3910 Walnut Street.
1898 Lodholtz, Edward, 3103 Diamond Street.
1903 Loeb, Leo, Medical Department, University of Pennsylvania.
1894 Loeb, Ludwig, 1421 North Fifteenth Street.
1902 Loeb, V. A., 1901 North Eighth Street.
1901 Longcope, W. T., Pennsylvania Hospital.
1875 Longstreth, Morris, 1416 Spruce Street.
1903 Ludlam, S. D., Friends' Asylum, Frankford, Pa.
1903 Lukens, G. L., Fifth Avenue and Fayette Street, Conshohocken, Pa.
1902 Luther, J. W., 412 South Fifteenth Street.

1896 McCarthy, D. J., 1329 Spruce Street.
1904 McClarey, Samuel, 308 South Fifth Street.
1880 McClellan, George, 1352 Spruce Street.
1901 McConnell, G., 1618 Pine Street.
1904 McCoombs, R. S., 2113 Chestnut Street.
1892 McFarland, J., 442 W. Stafford Street, Germantown.
1894 McKee, James H., 1519 Poplar Street.
1890 McKelway, George I., 114 South Eighteenth Street.
1902 McKenna, J. A., Highland and Baltimore Avenues, Lansdowne, Pa.
1894 McLeod, George, Ardmore, Pa.
1898 McReynolds, R. P., 3722 Walnut Street.
1902 Marshall, C. J., 2004 Pine Street.
1899 Masland, M. C., 2134 North Nineteenth Street.
1892 Massey, Frank, 3604 Locust Street.
1864 Mears, J. Ewing, 1429 Walnut Street.
1873 Meigs, Arthur V., 1322 Walnut Street.
1878 Mills, C. K., 1909 Chestnut Street.
1884 Mitchell, J. K., 1730 Spruce Street.
1896 Modell, D. A., 242 Fairmount Avenue.
1904 Moore, Joseph A., 146 Richmond Street.
1898 Morris, Henry, 313 South Sixteenth Street.
1885 Morrison, William H., 1821 Frankfort Avenue, Holmesburg, Pa.
1887 Morton, S. W., 1933 Chestnut Street.
1899 Müller, G. P., 1626 Spruce Street.
1880 Musser, J. H., 1927 Chestnut Street.
1898 Myers, A. W., Episcopal Hospital.

1879 Neff, J. S., 2300 Locust Street.
1903 Nesbit, V., 908 Pine Street.
1900 Newlin, A., 1702 Pine Street.

ELECTED
1898 Newton, R. D., 6137 Vine Street.
1902 Noble, C. P., 1509 Locust Street.

1894 O'Malley, Joseph, 2228 South Broad Street.
1900 O'Reilly, C., 1240 Erie Avenue.
1897 Ostheimer, Maurice, 1229 Locust Street.

1893 Packard, F. R., 1831 Chestnut Street.
1857 Packard, John H., Hotel Stenton (O. M.).
1900 Pancoast, H. K., University Hospital, University of Pennsylvania.
1901 Patterson, F. D., 1503 Locust Street.
1892 Pearce, F. S., 1407 Locust Street.
1900 Pearson, L., Veterinary Department, University of Pennsylvania.
1903 Pemberton, R. Children's Hospital.
1897 Pepper, William, 1811 Spruce Street.
1895 Perkins, F. M., 1428 Pine Street.
1897 Peters, L. C., 2136 Oxford Street.
1902 Pfahler, G. E., 1409 Spruce Street.
1901 Pickett, W., 1131 Spruce Street.
1885 Piersol, G. A., 4724 Chester Avenue.
1890 Potts, C. S., 1733 Chestnut Street.
1900 Prince, D. H., Jefferson Medical College.
1901 Purves, G. M., 750 South Tenth Street.

1901 Ranck, E. M., 107 Maine Street, Natchez, Miss.
1885 Randall, B. A., 1717 Locust Street.
1898 Ravenel, M. P., 908 Pine Street.
1904 Reber, Wendell, 1212 Spruce Street.
1894 Reckefus, C. H., 506 North Sixth Street.
1885 Reed, Boardman, Atlantic City.
1899 Reynolds, W., 27 South Indiana Avenue, Atlantic City.
1894 Rhein, J. H. W., 1732 Pine Street.
1903 Rhein, R. D., 2016 Pine Street.
1904 Rhoads, J. E., 2101 Chestnut Street.
1904 Rivas, Damaso, 5927 Girard Avenue.
1894 Riesman, David, 1624 Spruce Street.
1891 Ring, G. O., S. W. corner Nineteenth and Chestnut Streets.
1876 Roberts, John B., 1627 Walnut Street.
1884 Robertson, W. E., 912 North Fourth Street.
1902 Robins, Albert, 427 Brown Street.
1901 Robinson, E. T., 1326 Pine Street.
1904 Robinson, G. Cauley, Pennsylvania Hospital.
1889 Robinson, William Duffield, 2012 Mount Vernon Street.

ELECTED
1899 Rodman, W. L., 1626 Spruce Street.
1903 Roe, W. J., 1210 Locust Street.
1898 Rosenberger, R. C., 2330 North Thirteenth Street.
1894 Ross, George, 1721 Spruce Street.
1900 Roussel, A. E., 2112 Pine Street.
1900 Roxby, J. B., 2222 North Nineteenth Street.

1904 Sargent, A. Alonzo, 939 Spruce Street.
1896 Sailer, Joseph, 248 South Twenty-first Street.
1890 Sartain, Paul J., 212 W. Logan Square.
1895 Schamberg, J. F., 1636 Walnut Street.
1882 de Schweinitz, G. E., 1705 Walnut Street.
1904 Schumann, E. A., 15 Pelham Road.
1902 Schwerin, Justin C., 1625 Diamond Street.
1890 Scott, J. A., 1834 Pine Street.
1898 Sharpless, Wm. T., 100 South Church Street, West Chester, Pa.
1902 Shields, W. G., Jr., 412 West School House Lane, Germantown.
1889 Shoemaker, Harvey, 2011 Chestnut Street.
1895 Shumway, E. A., 2007 Chestnut Street.
1899 Sinclair, J. F., 216 South Forty-first Street.
1904 Singer, Benjamin L., 1914 North Eighteenth Street.
1902 Sinkler, Francis W., 348 South Sixteenth Street.
1868 Sinkler, Wharton, 1606 Walnut Street.
1901 Siter, E. D., 2038 Locust Street.
1881 Skillern, P. G., 241 South Thirteenth Street.
1903 Small, J. H., 914 South Forty-eighth Street.
1903 Smith, A. J., Medical Department, University of Pennsylvania.
1898 Smyth, Henry Field, Odessa, Delaware.
1902 Somers, L. A., 3554 North Broad Street.
1894 Spellissy, Joseph M., 110 South Eighteenth Street.
1896 Spiller, William G., 4409 Pine Street.
1904 St. John, E. Q., 1833 Chestnut Street.
1890 Stahl, B. F., 1502 Arch Street.
1901 Stanton W. B., 732 Pine Street.
1894 Steele, J. D., Fortieth and Locust Streets.
1889 Stengel, Alfred, 1811 Spruce Street.
1900 Stetson, J. B., 1329 Spruce Street.
1889 Stevens, Arthur A., 314 South Sixteenth Street.
1896 Stewart, Alonzo H., 250 North Twelfth Street.
1886 Stewart, David D., 1633 Spruce Street.
1904 Stilwagon, Thomas, Jr., Jefferson Medical College Hospital.
1899 Stout, G. C., 1726 Chestnut Street.
1884 Stritmatter, I. P., 999 North Sixth Street.

ELECTED
1869 Stryker, Samuel S., 3833 Walnut Street.
1894 Swan, John M., 3713 Walnut Street.
1902 Sweet, J. E., 62 East 116th Street, New York City.

1900 Talley, J. E., Fifty-sixth Street and Lansdowne Avenue.
1895 Taylor, A. E., University of California.
1897 Teller, Wm. H., 1713 Green Street.
1894 Thomas, W. Hersey, 1445 North Seventeenth Street.
1894 Thomson, Archibald G., 1426 Walnut Street.
1868 Thomson, William, 1426 Walnut Street.
1902 Thornton, E. Q., 922 Spruce Street.
1899 Tinker, M. B., Johns Hopkins Hospital, Baltimore, Md.
1902 Tracy, S. E., 1415 Walnut Street.
1897 Tucker, Henry, 112 South Twenty-first Street.
1898 Twaddell, Thomas, 4203 Chester Avenue.
1863 Tyson, James, 1606 Spruce Street.
1890 Tyson, T. Mellor, 1506 Spruce Street.

1900 Uhle, A. A., 1327 Jefferson Street.
1904 Ullman, J. T., 24 Carpenter Street, Germantown.

1895 Vandervoort, C. A., 3306 North Broad Street.
1887 Vansant, Eugene L., 1929 Chestnut Street.

1898 Wadsworth, W. S., The Covington, Thirty-seventh and Chestnut Streets, West Philadelphia.
1903 Walker, J. K., Pennsylvania Hospital.
1891 Wallace, James, 350 South Sixteenth Street.
1899 Walsh, J. P., 732 Pine Street.
1904 Walter, Georgianna, 3914 North Broad Street.
1890 Warder, C. B., 1715 Walnut Street.
1874 Warder, W. H., 1212 North Broad Street.
1903 Weber, C. H., 1308 Pine Street.
1903 Weisenburg, T. H., 2030 Chestnut Street.
1887 Westcott, T. S., 1833 Spruce Street.
1902 Wetherill, H. E., 3734 Walnut Street.
1897 White, Courtland Y., 334 South Sixteenth Street.
1873 White, J. William, 1810 South Rittenhouse Square.
1901 Whiteway, Harold M., 1924 Chestnut Street.
1893 Whiting, A. D., 1523 Spruce Street.
1905 Wieder, Henry S., 2131 North Fifteenth Street.
1868 Willard, De Forest, 1818 Chestnut Street.
1898 Willson, R. N., 350 South Fifteenth Street.

ELECTED
1869 Wilson, James C., 1437 Walnut Street.
1891 Wilson, Samuel M., 1517 Arch Street.
1891 Wilson, W. R., 112 South Twentieth Street.
1901 Winsor, Henry, in care of Winsor & Co., Piers 18 and 20, South Delaware Avenue.
1900 Wister, J. W., 5430 Main Street, Germantown.
1890 Wood, A. C., 128 South Seventeenth Street.
1898 Wood, George B., 129 South Eighteenth Street.
1865 Woods, D. Flavel, 1501 Spruce Street.
1899 Worden, C. B., 4208 Walnut Street.

1897 Yarrow, Thomas J., Jr., 1739 North Sixteenth Street.
1902 Yates, J. L., 4333 Ellis Avenue, Chicago, Ill.

1895 Zimmerman, Mason W., 1522 Locust Street.
1902 Zuirleck, A. J., 6236 Woodland Avenue.

NON-RESIDENT MEMBERS.

Baines, A. S., Jr., 4484 Finney Avenue, St. Louis, Mo.
Ball, M. V., Warren, Pa.
Breinig, P. B., Bethlehem, Pa.
Carter, W. S., Galveston, Texas.
Cerna, D., Galveston, Texas.
Dock, George, Ann Arbor, Mich.
Edwards, W. A., San Diego, Cal.
Egbert, Joseph P., Wayne, Delaware County, Pa.
Eskridge, J. T., Denver, Col.
Fox, J. M., Torresdale, Pa.
Gaylord, H. R., Buffalo, N. Y.
Hamaker, W. D., Meadville, Pa.
Hamann, C. A., 517 Euclid Avenue, Cleveland, Ohio.
Harris, H. F., Atlanta, Georgia.
Harrison, W. H., Harrisburg, Pa.
Hatch, John L., 2010 Fifth Avenue, New York City.
Hileman, J. B., Altoona, Pa.
Hiller, H. H.

Holder, C. A., Colorado Springs, Col.
Howard, F. H., Williamstown, Massachusetts.
Hunt, J. R., New York.
Izard, W., Camden, New Jersey.
Jamar, John H., Elkton, Md.
Lincoln, W. R., Cleveland, Ohio.
Muhlenberg, Frank, Reading, Pa.
Nancrede, C. B., Ann Arbor, Mich.
Osler, William, Johns Hopkins Hospital, Baltimore, Md.
Pease, H. D., Buffalo, N. Y.
Pfouts, G. B., Morris Plains, N. J.
Powell, W. M., Atlantic City, N. J.
Rahter, C. A., Harrisburg, Pa.
Rivas, Damoso, Lille, France.
Schreiner, E. R., U. S. A.
Slifer, Henry F., North Wales, Pa.
Smith, Allen J., Galveston, Texas.
Stadelman, E., Durango, Mexico.
Stiles, G. A., Conshohocken, Pa.
Stubbs, R. P., Wilmington, Delaware.
Taylor, A. E., University of California, San Francisco, California.
Taylor, L. H., Wilkesbarre, Pa.
Toulmin, H., Haverford, Pa.
Wells, G. M., Wayne, Delaware County, Pa.
Wetherill, R. B., Lafayette, Ind.
White, Frank, Elwyn.
Williams, H. L., Minneapolis, Minnesota.
Wilmarth, A. W., State Home for the Feeble-minded, Chippewa Falls, Wisconsin.
Ziegler, J. L., Mt. Joy, Pennsylvania.

CORRESPONDING MEMBERS.

ELECTED

1866 Bumstead, Freeman J., Deceased.
1859 Clark, Alonzo, New York. Deceased.
1898 Cornil, V., Faculté de Médecine, Paris, France.
1859 Dalton, J. C., New York. Deceased.
1885 Dent, Clinton T., Assistant Surgeon and Lecturer on Practical Surgery at St. George's Hospital, Surgeon to Belgrave Hospital for Children, London, England.
1860 Ellis, Calvin. Deceased.
1888 Fedeli, Gregorio, Rome, Italy.
1858 Flint, Austin, Sr. Deceased.
1890 Gibbes, Heneage, Ann Arbor, Michigan.
1858 Hammond, William A., New York. Deceased.
1860 Isaacs, Charles E., Brooklyn. Deceased.
1878 Jackson, J. B. S., Boston. Deceased.
1886 Pye-Smith, P. H., Physician and Lecturer on Medicine at Guy's Hospital, London, England.
1860 Reeves, James E., Wheeling, West Virginia. Deceased.
1861 Rokitansky, Carl. Deceased.
1898 Virchow, Rudolf, Berlin, Germany. Deceased.
1860 Watson, John, New York. Deceased.
1898 Welch, William H., Professor of Pathology, Johns Hopkins University, Baltimore, Maryland.
1859 Worthington, Wilmer, West Chester, Pennsylvania. Deceased.

Proceedings

of the

Pathological Society of Philadelphia.

JANUARY, 1904. NEW SERIES, VOL. VII., NO. 1.

TABLE OF CONTENTS.

Fourth Annual Exhibition Meeting.—ROSENBERGER, The Actual and Comparative Resistance of Acid-fast Bacilli.—BEHREND, Report of a Case of Brain Tumor and of a Case of Ruptured Tubal Pregnancy.

Fourth Annual Exhibition Meeting.

The fourth annual exhibition meeting of the Pathological Society of Philadelphia was held in the Mütter Museum of the College of Physicians, January 14, 1904. The names of the exhibitors together with the specimens exhibited are given below.

Dr. B. M. Anspach.

Chronic pelvic peritonitis. Ovaries of two sides joined together back of the uterus. Condition following vaginal puncture.

Intramural fibroid tumor of uterus with carcinoma of endometrium.

Subperitoneal fibroid tumors of uterus. Adenocarcinoma of endometrium.

Drs. J. G. Clark and **B. M. Anspach.**

Adenocarcinoma of ascending colon. Resection of bowel and enterorrhaphy by means of Connell suture.

Adenocarcinoma of fundus of uterus. Pyometra.

Adenocarcinoma of ovary.

Adenoma malignum, diagnosed from curettings.

Carcinoma at ileocecal junction. Adenocarcinoma. Resection at head of colon, vermiform appendix, and terminal portion of ileum.

Carcinoma of breast with enlargement of lymphatic glands.

Dermoid cyst of ovary.

Extrauterine pregnancy.

Metastatic growth of endometrium from bilateral psammomatous papillary cyst of ovary.

Multilocular cyst of ovary.

Perforating carcinomatous ulcer of stomach. Partial gastrectomy.

Squamous carcinoma of cervix. Panhysterectomy.

Drs. J. G. Clark and **C. C. Norris.**

Acute suppurative appendicitis.

Appendix containing fecal concretions.

Catarrhal appendicitis.

Catarrhal appendicitis. Perioophoritis. Ovaries show corpus luteum.

Periappendicitis with adhesions of tip.

Dr. W. M. L. Coplin.

Lung of rat, showing striped muscle fibers in wall of vessel.

Drs. W. M. L. Coplin and **Lieutenant James F. Carroll, U. S. A.**

Yeast cell in stomach of mosquito.

Drs. W. M. L. Coplin and **A. G. Ellis.**

Trypanosoma Lewisi; blood of wild gray rat.

Trypanosoma Lewisi; spreads from bone-marrow of rat.

Drs. W. M. L. Coplin and **John Funke.**

Brain. Secondary sarcoma, showing hemorrhage.

Cerebellum. Gliosarcoma.

Intestine. Typhoid ulcer.

Kidney. Chronic interstitial nephritis.

Lung. Anthracosis.

Lung. Croupous pneumonia.

Lymph-nodes from Hodgkin's disease.
Spleen Acute miliary tuberculosis.
Spleen. Infarction.
Peritoneum. Acute tuberculosis.
Thrombosis of internal iliac artery and vein. (Two specimens.)

Drs. W. M. L. Coplin and **Henry E. Radasch.**
Human embryo, 6 to 7 weeks.

Dr. M. H. Cryer.
Typical skulls, the sagittal section showing four nasal meatuses.
Coronal sections showing variations in shape and size of maxillary sinuses in different individuals, and on the two sides in the same individual.
Enlarged frontal sinuses.
Sagittal section showing four nasal meatuses.
Variations in size and shape of nasal fossæ.
Enlarged antrums.
Variations in size of antrum of Highmore.

Dr. Judson Daland.
Heart. Sacculated aneurysm of the arch of the aorta containing old and recent clots. Chronic fibroid aortic valvulitis with left ventricular hypertrophy and dilatation.
Heart. Dissecting aneurysm of the thoracic aorta rupturing into the pericardial sac.
Heart. Extreme dilatation of the left ventricular cavity, and aneurysmal dilatation of the apex of the left ventricular cavity, the wall of which is composed of two layers of pericardium.
Heart. Aneurysm and dilatation of the left ventricle with thrombosis of the left coronary artery and fibroid degeneration.
Heart. Fibroid degeneration of the interventricular septum and anterior papillary muscle.
Heart. Extreme endarteritis going on to the formation of three small aneurysms. Dilatation of the left ventricular cavity.
Heart. Vegetative aortic valvulitis. Mitral stenosis. Pericarditis.
Heart. Aortic stenosis with calcareous deposit and hypertrophy of the left ventricle.

Heart. Tricuspid and mitral stenosis.

Heart. Fatty degeneration and infiltration.

Heart. Ulcerative endocarditis destroying the aortic leaflets.

Trachea. Papilloma.

Dr. Clifford B. Farr.

Liver and spleen from a case of so-called Banti's disease. Also ruptured esophageal varix. Splenic anemia, third stage of Osler.

Drs. Charles H. Frazier and **George P. Müller,** from the Laboratory of Surgical Pathology; charts used in demonstrating the pathology of surgical affections in the course on surgical pathology, University of Pennsylvania.

Benign enlargements of the thyroid gland.

Carcinoma of the breast.

Adenofibroma and intracanalicular papillary fibroma of the breast.

Acute catarrhal and interstitial appendicitis.

Acute ulcerative and interstitial appendicitis.

Chronic interstitial and obliterative appendicitis. Foreign bodies in appendix.

Sarcoma of long bones.

Carcinoma of inframaxillary bone.

Sequestration and necrosis of bone.

Dr. Goldberg, from the Pathologic Department of the Wills Eye Hospital.

Cystic degeneration of the iris following wound in ciliary region.

Phthisis bulbi following explosion.

Phthisis bulbi. Calcareous degeneration of lens; ciliary wound.

Phthisis bulbi. Calcareous lens.

Punctured wound of eyeball. Prolapsed iris; traumatic cataract.

Phthisis bulbi (14).

Black cataracts (3).

Ciliary wound. Calcareous degeneration of cornea.

Wound of cornea, prolapse of contents of eyeball (gradual).

Glaucoma; bullous keratitis.

Panophthalmitis.

Ciliary staphyloma and cyclitis.

Phthisis bulbi. Solid mass of bone in center of globe.

Panophthalmitis following cataract extraction.

Ciliary wound. Foreign body in eyeball.

Melanotic sarcoma of choroid.

Mules' stump; enucleated for sympathetic irritation (11 mos.).

Enucleation for sympathetic irritation. Scleral wound.

Chronic glaucoma; deep cupping; choroidal atrophy.

Phthisis bulbi. Calcareous degeneration of choroid.

Corneal staphyloma and thickening (3).

Contusion of globe.

Iridoscleritis.

Panophthalmitis (5).

Secondary glaucoma.

Chronic iridocyclitis following cataract extraction.

Chronic iridocyclitis.

Traumatic iridocyclitis; calcareous lens.

Foreign body in vitreous.

Traumatic iridocyclitis (4).

Uveitis.

Incipient panophthalmitis following injury.

Incipient panophthalmitis; foreign body in vitreous twenty-four hours after injury.

Corneal staphyloma.

Chorioretinitis.

Glioma of optic nerve and retina.

Phthisis bulbi. Calcareous degeneration, choroid and lens; small, well-formed calcareous node in vitreous chamber, surrounded by area of hemorrhage.

Glioma retinæ. Optic nerve involvement.

Panophthalmitis; corneal perforation (coal injury).

Incipient panophthalmitis (6).

Glioma retinæ.

Iridocyclitis. Retinal cyst.

Sloughing keratitis.

Iridocyclitis. Old abscess of cornea.

Iridocyclitis. Dislocation of lens into anterior chamber.

Foreign body in retina.

Corneal ulcer. Hypopyon.

Intercalary staphyloma (buphthalmus); ophthalmia neonatorum.

Panophthalmitis; corneal wound; prolapsed iris.

Secondary hemorrhagic glaucoma.

Ciliary staphyloma. Panophthalmitis (coal injury).

Phthisis bulbi. Calcareous changes in lens and choroid ciliary wound ten years ago.

Spindle-celled sarcoma.

Small round-celled melanosarcoma of choroid.

Sarcoma of choroid perforation of globe by growth.

Traumatic iridocyclitis, calcareous lens.

Foreign body in ciliary region.

Foreign body in eyeball (2).

Foreign body in vitreous, encapsulated.

Foreign body penetrating cornea, iris, and lens.

Chronic glaucoma; sympathetic irritation.

Chronic glaucoma in which four posterior sclerotomies had been done. The retina was pathologically detached everywhere except at points of puncture.

Chronic glaucoma. Lens dislocated into macular region; couching operation done about twenty years ago.

Chronic glaucoma. Anterior staphyloma.

Cystosarcoma of orbit.

Phthisis bulbi. Subconjunctival hypertrophy.

Melanotic sarcoma of choroid.

Spindle-celled sarcoma of choroid.

Melanotic sarcoma of choroid.

Small round-cell melanosarcoma of choroid.

Sympathetic irritation.

Chronic glaucoma (4).

Iridocyclitis following injury.

Old iridocyclitis (2).

Elephantiasis of lids.

Traumatic rupture of globe.

Panophthalmitis; rupture of globe.

Chronic glaucoma. Patch of choroidal atrophy.

Complete ossification of choroid.

Panophthalmitis; spontaneous rupture of globe in orbit during typhoid fever.

Drs. H. R. M. Landis and **F. A. Craig**, from the Henry Phipps Institute.

Large white kidney with cyst. (Two specimens.)

Miliary tubercles in suprarenal glands.

Tuberculous ulcers of intestines.

Beginning ulceration of larynx.

Tuberculous necrosis of arytenoid cartilage.

Amyloid spleen.

Tuberculous epididymitis.

Tuberculous ulcers of intestines.

Obliterative pericarditis.

Hydronephrosis with calculus in situ.

Tuberculous mesenteric glands.

Fatty liver.

Cavity of recent formation; tuberculous infiltration.

Ruptured bloodvessel in cavity resulting in death.

Cavity; thickened pleura; pulmonary tuberculosis.

Old caseous area at apex; tuberculous infiltration with fibrous formation, healthy lung at base; enlarged bronchial glands.

Walled-off cavity; miliary tuberculosis.

Ulceration; recent infiltration; healthy lung.

Tuberculous focus in kidney.

Dr. R. S. Levenson.

Cast of hands. Specific dactylitis.

Cast of hand. Clubbed fingers.

A series of casts of the deformities of rheumatoid arthritis.

Dr. W. T. Longcope, from the Ayer Clinical Laboratory, Pennsylvania Hospital.

Congenital atresia of aorta. Patent ductus arteriosus; thrombosis of right axillary and subclavian veins.

Acute vegetative mitral endocarditis. Produced by inoculation

of streptococcus obtained from case of rheumatism, chorea, and endocarditis. Anemic infarction of kidney.

Rabbit 4. Intravenous inoculation of streptococcus from rheumatic endocarditis and chorea. Section through synovial membrane of ankle-joint.

Arthritis of ankle of rabbit. Produced by intravenous inoculation of streptococcus obtained from blood of case of rheumatism, chorea, and endocarditis.

Tuberculosis of uterus, Fallopian tubes, and urinary bladder.

Hydronephrosis. Occlusion of ureter and pelvis by calculus.

Aneurysm of heart. Calcification and occlusion of descending branch of left coronary artery.

Aneurysm of descending arch of aorta. Rupture into esophagus.

Two aneurysms (sacculated). Arch of aorta.

Aneurysm of heart; rupture into pericardial cavity. Occlusion of descending branch of left coronary artery.

Rabbit 3. Smears from vegetations on mitral valves.

Rabbit 3. Kidney showing hemorrhages and masses of cocci in glomerular capillaries and small vessels.

Dr. D. J. McCarthy. From the William Pepper Clinical Laboratory and the Laboratory of the Henry Phipps Institute.

Defective development of right brain; occipital lobe.

Tumor of pituitary gland. Adiposis dolorosa.

Aneurysm of anterior cerebral artery.

Tumor of pituitary, with involvement of sella turcica.

Tuberculous tumor of crus. Crossed paralysis third nerve.

Tumor of pituitary. Enlargement of adrenals.

Cyst of pituitary body. Tuberculosis; no acromegaly.

Traumatic epilepsy. Adhesion of meninges to brain.

Aneurysm of internal carotid near sella turcica. Acromegaly.

Tuberculosis of spinal meninges. A soft gelatinous exudate on membranes.

Ruptured aneurysm of posterior cerebral artery.

Tumor of pituitary with hydrocephalus.

Traumatic epilepsy.

Pott's disease.

Aneurysmal dilatation of basilar artery with arteriosclerosis of circle of Willis.

Drs. J. McFarland and **Guthrie McConnell**, from the Pathologic Laboratories of the Medico-Chirurgical College.

Ovary. Hyaline degeneration of bloodvessels.

Fallopian tube. Tuberculosis.

Uterus. Chronic endometritis. Small submucous myoma. The endometrium has atrophied on account of the pressure exerted by the myoma.

Fallopian tube. Purulent salpingitis.

Fallopian tube. Catarrhal salpingitis.

Ovary. Cyst of ovary.

Ovary. Tuberculosis.

Ovary. Ripe ovum in Graafian follicle.

Fallopian Tube. Ectopic gestation.

Vagina. Fibrous polyp.

Uterus. Chorion villi and decidual cells from a case of abortion.

Vagina. Sarcoma. From a child.

Vagina. Elephantiasis (syphilitic).

Vagina. Cyst of labium minus. Contains glands resembling those of the endometrium.

Vagina. Giant-cell carcinoma.

Uterus. Chronic glandular endometritis.

Uterus. Erosion of cervix.

Uterus. Isolated Müller's duct.

Uterus. Myometrium four weeks after an hydatid mole. Shows wandering chorion cells.

Uterus. Tuberculosis of endometrium.

Uterus. Myoma.

Ovary. Multilocular cyst.

Uterus. Medullary carcinoma of the corpus. The cancer cell nests are breaking into the glandular spaces.

Fallopian tube. Hematosalpingitis.

Fallopian tube. Carcinoma.

Uterus. Sarcoma (necrotic).

Uterus. Adenocarcinoma of the corpus.

Uterus. Chorioepithelioma or deciduoma malignum. (Two specimens.)

Uterus. Sarcoma of the corpus. Composed of polymorphic cells.

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Uterus. Polyp of the cervix—adenofibroma.

Fallopian tube. Endoperisalpingitis.

Fallopian tube. Extrauterine tubal pregnancy. The tube is filled with blood. The chorionic villi show well in the blood clot.

Ovary. Papillary adenocystoma.

Ovary. Sarcoma. (Myxangiosarcoma tubulare.)

Ovary. Small round-cell sarcoma.

Ovary. Sarcoma (round-cell).

Ovary. Sarcoma (spindle-cell).

Ovary. Adenocystoma (malignant).

Ovary. Adenocystoma (malignant). Contains cells similar to those of squamous epithelium, and also giant cells.

Ovary. Teratoma. (Three specimens.)

Ovary. Dermoid cyst.

Ovary. Cystic corpus luteum. Notice how beautifully the germinal epithelium on the surface of the ovary is shown.

Ovary. Corpus luteum, showing point of rupture.

Ovary. Cyst of the parovarium.

Ovary. Cystic degeneration (hemorrhagic).

Drs. Geo. P. Müller and **William H. MacKinney**, Pathologic Institute of the German Hospital.

Perforated ulcer upon the anterior wall of the stomach.

Strangulated femoral hernia (omentum and sac).

Hypernephroma at lower pole of left kidney.

Cystic papilloma of ovary.

Acute calculus cholecystitis.

Chronic calculus cholecystitis.

Carcinoma of ovary.

Tubal pregnancy.

Fatty cirrhosis of the liver.

Tuberculosis of lung.

Acute pancreatitis, fat necrosis of omentum.

Hypertrophy and dilatation of the heart. Aortic insufficiency, mitral stenosis and insufficiency, relative tricuspid insufficiency. Atheroma of aorta.

Abscess of liver, secondary to suppurative cholangitis.

Squamous carcinoma of the rectum.

Drs. B. M. Randolph and **Guthrie McConnell**, from the Laboratories of the Philadelphia Polyclinic Hospital.

Melanotic myxofibrosarcoma of subcutaneous tissue of leg. Hematoxylon.

Fibromyxosarcoma of abdominal wall.

Endothelioma of dura, invading parietal bone.

Fibrosarcoma of intestine with inflammatory changes. Many eosinophiles.

Fibroadenosarcoma of kidney.

Endothelioma of foot. Derived by proliferation of cells lining lymph spaces of the corium.

Perithelioma of lower jaw.

Endothelioma of the inferior maxilla.

Angiosarcoma of ethmoid.

Giant-celled sarcoma of alveolar process. (Epulis.)

Giant-celled fibrosarcoma of wrist.

Large round-celled sarcoma of antrum of Highmore.

Spindle-celled sarcoma with fatty degeneration; from submucous tissue of mouth.

Melanotic fibrosarcoma of the gluteal region.

Melanotic alveolar sarcoma of axillary gland.

Fibromyxosarcoma of the inguinal region with acute inflammatory infiltration.

Myxomatous melanotic round-celled sarcoma of thigh.

Lymphangiosarcoma of lymph-node of submaxillary region.

Dr. M. P. Ravenel, from the State Live Stock Sanitary Board.

Tissues of calf not protected by injections of human tubercle bacillus. Control to next specimen.

Tuberculous ulceration of tonsils of pig fed with pure culture of human tubercle bacillus. The intestine was free from disease.

Lung of cow. Experimental tuberculosis.

Tuberculous mass formed of intestine and mesenteric glands

from a child. The culture obtained was virulent for a calf, causing death in thirty-four days.

Tuberculosis in calf produced by inoculation of culture obtained from mesenteric gland of a child.

Tuberculosis in six-year-old cow produced by inoculation of culture obtained from mesenteric gland of a child.

Lungs and intestines of monkey injected with tuberculosis by feeding pure culture of tubercle bacillus (2).

Lung of sheep, showing nodules due to a parasitic worm (strongylus pulmonalis).

Tuberculosis. Chest-wall of calf infected with human tuberculosis.

Liver, spleen, and lungs of monkey infected with tuberculosis by inoculation.

Tuberculosis of larynx of cow. Natural infection.

Tuberculosis of spleen of cow. Natural infection.

Lung of cow showing cavity formation. Infection by feeding.

Lung of calf infected with human tuberculosis.

Tuberculosis. Lung of cow showing type of lesion known as "grape disease." Natural infection.

Lung of steer inoculated with culture obtained from mesenteric gland of child.

Lungs of pig infected by feeding pure culture of human tubercle bacillus. The intestine was free from disease.

Tissues of calf immunized by inoculation with human tubercle bacillus, then inoculated with a virulent bovine culture.

Drs. David Riesman and **A. G. Ellis.**

Multiple amebic abscesses of liver. The case will be reported in detail later.

Multiple amebic abscesses of liver.

Multiple amebic abscesses of liver.

Dr. William E. Robertson, from the Laboratory of the Episcopal Hospital.

Aneurysm of ascending, transverse, and part of the descending aorta. Tuberculosis of the lungs. Progressive weakness, cough,

bloody expectoration, dyspnea and dysphagia, pulsating mass about left sternoclavicular region, large dull area over upper left chest posteriorly.

Aneurysm of innominate artery. Man, aged thirty-nine; only ceased work two weeks before death, on account of orthopnea. At autopsy trachea was found compressed and the aneurysm had almost perforated at that part nearest to the trachea.

Aortic vegetations, cirrhosis of liver.

Buttonhole mitral valve, sclerotic and incompetent aortic cusps with a few vegetations upon them. Cyanotic induration of the organs, cirrhotic liver and kidneys. Right kidney had two ureters separate down to bladder.

Carcinoma of lower end of the esophagus, tuberculosis of the lungs. Male, aged forty-eight. Esophageal bougie met an obstruction fifteen inches from the front teeth.

Carcinoma of stomach, rupture, abscess between stomach and spleen.

Enormous primary growth of the pleura, probably an endothelioma; heart pushed well over into right side of chest. Some secondary nodules in the lungs. Photograph taken about ten months before death shows growth pushing between ribs of left chest, but before it assumed the enormous proportions subsequently reached.

Extensive colloid carcinoma of abdominal viscera. Tuberculosis of the lungs.

Hour-glass contraction of stomach.

Hypernephroma, obstruction of ascending vena cava. Clinically, hematuria, hemoglobinuria, albuminuria, albumosuria.

Hypertrophy of heart; two aortic and two pulmonary cusps adherent and sclerotic. High degree of interstitial nephritis, kidneys cystic, liver cirrhotic. Miliary tuberculosis of the lungs. Precordial pain; loud blowing murmur at apex and at aortic cartilage, both systolic in time. Sudden death.

Myelitis, retention of urine, cystitis, pyelitis, abscesses of the kidneys, stone in the bladder, enlargement of middle lobe of the prostate.

Pulmonary vegetations. In the same case were found localized

empyema, infarcts of the lungs, purulent bronchitis, hour-glass contraction of stomach. Cultures from lungs showed pneumococci.

Small round-celled sarcoma of small bowel. Purulent peritonitis. Boy five years of age. External fistulous opening followed operation, with discharge of partially digested food.

Traumatic rupture of the liver. Fluid blood in peritoneal cavity. Male, aged thirty-two; caught between two wagons. No external evidence of injury.

Typhoid fever complicated with Ludwig's angina. Streptococcus recovered from the edematous tissue of the larynx.

Typhoid perforations healed by an omental adhesion. A second perforation occurring some days later caused peritonitis and death. This case is of interest owing to the age (eleven years), and, further, because it furnishes indubital evidence that perforation may recover spontaneously.

Typhoid ulcers of the intestine. Involvement both of Peyer's patches and of the solitary follicles.

Ulcerated endocarditis with dilatation of heart. Contracted gonorrhea six weeks before fatal issue. Developed gonorrhea arthritis of right knee and both ankle-joints. Heart lesion, general sepsis.

Unsuspected carcinoma of lesser curvatures of stomach, cystic kidneys, general arterial thickening, hypertrophy of heart. Male, aged eighty; healed tuberculous focus in upper lobe of right lung.

Dr. Randle C. Rosenberger, from the Pathologic Department of the Philadelphia Hospital.

Aneurysm of aorta.

Aneurysm of heart.

Atrophic cirrhosis of liver.

Buttonhole, mitral (2).

Carcinoma of esophagus. Tuberculous ulcers were present in the large intestine.

Carcinoma of stomach (3).

Carcinomatous nodules in heart.

Carcinosis of diaphragm.

Carcinosis of liver, stomach, pancreas, peritoneum, and diaphragm.

Chronic interstitial nephritis.

Chronic parenchymatous nephritis.

Gangrene of lung. Acid-fast bacilli found in sputum.

Hemorrhage of cerebellum.

Hemorrhage into the pericardium.

Perforation of appendix at apex.

Portion of cerum removed at operation. Result of volvulus.

Pulmonary valve of heart with two leaflets.

Tuberculosis of pericardium. Cross-section of heart near apex.

Tuberculosis of peritoneum.

Typhoid ulcers.

Ulcerative endocarditis.

Drs. J. F. Schamberg and **N. Gildersleeve.**

Anchorion Schönleinii. Fungus of tinea favus. (On glycerin agar; two weeks' growth.)

Anchorion Schönleinii. Fungus of tinea favus. (On maltose agar; two weeks' growth.)

Anchorion Schönleinii. From favus of scalp. (On maltose agar; two weeks' growth.)

Anchorion Schönleinii. From favus of scalp. (On glycerin agar; two weeks' growth.)

Anchorion Schönleinii. From favus of hand. (On maltose agar; two weeks' growth.)

Anchorion Schönleinii. From favus of hand. (On glycerin agar; two weeks' growth.)

Ringworm. Large spore from case of barbers' itch. (On glycerin agar.)

Ringworm fungus. Large spore from arm. (On maltose agar.)

Ringworm. Large spore from case of barbers' itch. (On maltose agar.)

Ringworm fungus. Large spore from arm. (On glycerin agar.)

Ringworm fungus. Microsporon Audouini from ringworm of scalp. (On maltose agar.)

Ringworm fungus. Microsporon Audouini from ringworm of scalp. (On glycerin agar.)

Ringworm fungus from scalp.

Drs. G. E. de Schweinitz and E. A. Shumway.

Absolute glaucoma; bullous keratitis.

Absolute glaucoma; bullous keratitis. Metallic foreign body retained in eye for years.

Black cataract. Patient was highly myopic, and had extensive myopic retinochoroiditis.

Chorioretinitis and extensive pigmentation of the retina. Patient blind from birth.

Hyaline degeneration of corneal scar. Van Gieson stain.

Infected ulcer of cornea; perforation and prolapse of iris; secondary glaucoma.

Intraocular foreign body. Piece of copper.

Sarcoma of choroid; extrascleral mass.

Secondary pigmentation along retinal vessels in chronic chorioretinal atrophy.

Shrunken eyeball; hyaline and calcareous deposits in cornea.

Traumatic iridocyclitis, with exudates behind lens, which is cataractous, caused by foreign body (steel) in vitreous; removed with magnet, but enucleation required later.

Traumatic iridocyclitis caused by injury by piece of steel, which was in eye eleven days before removal with magnet; cataract and exudate posterior to lens.

Traumatic iridocyclitis, after injury by piece of steel.

Dr. E. A. Shumway.

Pigmentation of retinal capillaries in case of recurrent intraocular hemorrhage.

Dr. William G. Spiller, from the William Pepper Clinical Laboratory.

Arrest of development of brain.

Endothelioma of motor area (2).

Fibromas of ulnar nerve.

Fibromas of plantar nerve.

Hemiplegia, hemianesthesia, and hemianopsia due to multiple lesions of brain.

Hemorrhage of the pons.

Hemorrhage in optic thalamus.

Infiltrating tumor of motor area of brain.

Meningitis in plaques of parietal lobe.

Multiple sarcomatosis.

Sarcoma of brain.

Sarcoma of centrum semiovale.

Sclerosis of parietal, occipital, and temporal lobes.

Sinus thrombosis.

Softening of occipital lobe.

Tubercle of pons.

Tumor of cerebellopontile angle.

Tumor of optic chiasm, causing bitemporal hemianopsia.

Dr. George C. Stout.

Abscess of brain.

Dr. John M. Swan.

Anomalies of the renal arteries. (Seven specimens.)

Anomalies of the renal arteries. (Six specimens.)

Anomalies of the renal arteries. Double renal arteries, upper arising just below superior mesenteric, lower above bifurcation of aorta.

Anomalies of the renal arteries. Horseshoe kidney with eight arteries.

Anomalies of the renal arteries. Three renal arteries on each side on the left lowest branch arises from common iliac.

Dr. C. Y. White, from the Children's Hospital.

Abscess of lung.

Pleurisy.

Pleurisy and pneumonia.

Pneumonia.

From the William Pepper Laboratory of Clinical Medicine.

Abscess of heart-wall and base of valve.

Actinomycosis of cow.

Acute lymphatic leukemia.

Chronic acetanilid poisoning. (Two specimens.)

Chronic lymphatic leukemia.

Cirrhosis of liver.

Cystic kidney. Chronic parenchymatous nephritis.

Fibroid phthisis; plastic pleurisy.

General tuberculosis. Monkey.

Karyokinesis of erythroblast. Daughter stage (early).

Karyokinesis of erythroblast. Daughter stage. (Two specimens.)

Karyokinesis of erythroblast. Early stage. (Three specimens.)

Perforating empyema. Necrosis of rib.

Pernicious anemia. Basic granulation.

Pernicious anemia. Irregularity in size.

Pernicious anemia. Normoblast showing pyknosis.

Sarcoma (spindle-cell) of kidney with metastasis to liver.

Tuberculosis of liver. Monkey.

Tuberculosis of lung.

Tuberculosis of monkey. Mild infection.

Tuberculosis of omentum. Monkey.

Drs. M. W. Zimmerman and **E. A. Shumway.**

Sarcoma of choroid.

The Actual and Comparative Resistance of Acid-fast Bacilli.

RANDLE C. ROSENBERGER, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

No more interesting group of bacteria has ever been isolated than that which is known as the acid-fast group. It comprises quite a few organisms, among them being some isolated from butter, some from milk, others from grass; while the lepra bacillus, the smegma bacillus, the bacillus of syphilis (Lustgarten), and the tubercle bacillus are also included in the group.

All of these have been successfully cultivated and studied, with the possible exceptions of the bacillus of leprosy, the bacillus smegmatis, and the so-called bacillus of syphilis. The latter organisms are claimed by some to have been cultivated, but by most observers these assertions are denied.

Courmont and Potet[1] have tabulated a list of acid-fast bacilli as regards their origin:

1. A. Pathogenic.

B. tuberculosis.
B. lepræ.

B. Non-pathogenic.

(*a*) Upon the lips.
(*b*) B. smegmatis.
(*c*) B. ceruminis.
(*d*) B. nasal mucus.

2. In Diseases of Man.

(*a*) Gangrene of lung.
(*b*) Conjunctivitis.
(*c*) Genitourinary diseases.
(*d*) Feces from typhoid.
(*e*) Leprosy.
(*f*) Tuberculosis.

In Animals.

1. Human, avian, bovine, and piscian t. b.
2. B. Moeller.
3. Calves' smegma.
4. Mist B.

In Butter.

(*a*) Petri Rabinowitsch.
(*b*) Korn.
(*c*) B. Coggi.
(*d*) B. Tobler (i., ii., iii., iv., v.).
(*e*) B. Markl.
(*f*) B. Minot.
(*g*) Moeller's milk B.

In Nature.

1. Upon Plants.
   (*a*) Timothy B. Moeller.
   (*b*) Grass B. Moeller.
2. In Earth.
   (*a*) Sewage (Spina-Houston).
   (*b*) Earth (Karlinski-Moeller).
3. Mist B.

The resemblance these organisms possess are principally in morphologic and tinctorial properties, the cultures differing very markedly as regards the time of appearance of the growth after inoculation.

Moeller[2] regards the butter and milk bacilli, which are resistant to acids, as varieties of the grass bacilli II., in consideration of the fact that they have a common habitat. He also cultivated from milk in pure culture an organism which he has named the timothy bacillus. It is a slender rod, sometimes slightly curved, which, microscopically, is often impossible to distinguish from the tubercle bacillus. In the decolorizing solution, as well as in sections with the ordinary staining methods, it behaves exactly like the tubercle bacillus.

Besides these organisms he mentions a "manure bacillus" which bears a morphologic and tinctorial resemblance to the timothy bacillus. In growth of cultures and in pathogenesis it also resembles the grass bacillus II.

Grassberger, Korn, and others have isolated acid-resisting bacilli from butter and grass.

Capaldi isolated a bacillus from cows' dung which resembled the Petri Rabinowitsch butter bacillus. Severin found similar bacilli in horses' dung; Ferran in cows', horses', and human feces. Acid-resisting bacilli have also been encountered in the human intestine by von Jaksch.

Novy mentions acid-resisting bacteria occurring in the conjunctiva.

Alvarez and Tavel were the first to observe an acid-resisting bacillus in smegma, and called it the bacillus smegmatis. Laser and Czeplewski claim to have obtained this organism upon artificial culture media.

Cowie,[3] in making observations upon the smegma bacillus of man and also of the lower animals, finds that acid-resisting bacilli are found in the smegma of the horse, cow, dog, guinea-pig, and white rat. In the rabbit and cat no such organisms exist. He claims that the human smegma bacillus resists a 25 per cent. solution of nitric acid for ten minutes; absolute alcohol decolorizes the organism in ten seconds.

He quotes Zahn as noticing the presence in non-tuberculous

sputum of acid-resisting bacilli; while A. Fraenkel and Rabinowitsch observed acid-fast bacilli in sputum from cases of pulmonary gangrene. Moeller also found acid-resisting bacilli in non-tuberculous sputum.

Ophüls[4] reports five cases of gangrene of the lung, in the lesions of which acid-proof bacilli were found. In the first case the bacilli were slender, stained irregularly, arranged in short threads with true branching. The organisms were frequently arranged in dense clusters and stained poorly with methylene blue, better in dilute carbol fuchsin and by Gram's method. They were decolorized by a 1 per cent. solution of hydrochloric acid in 60 per cent. alcohol. When sections were treated with 25 per cent. sulphuric acid and mounted in glycerin in order to avoid the alcohol, they remained stained. They stained better when a 12½ per cent. solution of sulphuric acid was used. They were not obtained in culture. Glycerin agar-agar was the only medium used for inoculations.

In the second case bacilli were found which resembled very much those found in Case I. These bacilli grew upon glycerin agar in the form of moist, grayish-white colonies for the first generation, but no further growth could be obtained while under aerobic or anaerobic conditions.

In the third case large numbers of acid-proof bacilli were observed. In the walls of the cavity the organisms grew in the form of S-shaped bunches very much like the tubercle bacillus. The bacilli did not grow on ordinary media.

The fourth case also showed in the areas of disease and in spreads acid-proof bacteria. They were not obtained in culture.

In the fifth case acid-proof bacilli were found in the diseased areas, which organisms resembled those found in the four previous cases. They were not obtained by ordinary methods of cultivation.

Benvenuti[5] found in the sputum of a case of pulmonary gangrene acid-proof bacilli which were mistaken for tubercle bacilli. Postmortem examination showed, however, a complete absence of tuberculous lesions.

Mayer,[6] in fifty-eight cases of gangrene of the lung, found in the sputum of ten acid-proof bacilli which were not tubercle

bacilli and which he classifies as streptothrices. He also obtained them in culture, the growth being a wrinkled white layer. They were not pathogenic for animals.

Foli,[7] in six cases of gangrene of the lung, found acid-fast bacilli in three. He was able to differentiate the true tubercle bacillus from the acid-fast organisms by means of a solution of tartaric acid (1 : 20). (Whether an alcoholic or watery solution is not stated.) He claims that the "pseudotubercle bacilli" decolorize in five minutes, while the true tubercle bacillus requires twenty minutes for its decolorization.

The bacillus of avian tuberculosis resists acids and differs from the mammalian tubercle bacillus in the appearance of cultures and the temperature conditions, thriving well at 42° C., while the organism of mammalian tuberculosis does not.

The bacilli of fish and bovine tuberculosis also resist acids, the latter more markedly than the former.

Klein and Marmorek have shown that all tubercle bacilli are not acid fast, as in young bacilli which have not yet been covered with the peculiar fatty matter found in older bacilli decolorization takes place with acid solutions.

Borrel claims that after long action of warm xylol upon the tubercle bacillus he separated a mass which was resistant to acids and alcohol, while the tubercle bacilli thus treated lost their acid-fast properties.

Abbott and Gildersleeve,[8] in an article upon the etiologic significance of the acid-resisting group of bacteria, remark that all of these bacilli resist "for longer or shorter periods" solutions of acids. For example, they resist "5 per cent. acetic acid and alcohol, hydrochloric acid 3 per cent. and alcohol, sulphuric acid 5 per cent. in water, but are decolorized almost instantly if treated with nitric acid 25 to 30 per cent."

Pseudotubercle bacilli have been found not only in sputum, but also in mucus from the nose and pharynx, coating of the tongue, sordes on the teeth, as well as in the secretion upon the tonsils.

Rappin and Henrot,[9] in four cases of syphilis, isolated a bacillus in the urine, very pleomorphic, and possessing acid-fast properties resembling the bacillus of Lustgarten.

Macé claims that the smegma bacillus will not resist glacial

acetic acid for two minutes, but the human tubercle bacillus will. If the B. smegmatis is treated with a 5 per cent. solution of caustic soda in alcohol the acid-fast property is lost, but this property is said to be not affected in the B. tuberculosis. These facts the writer can fully substantiate by the experiments included in the tables.

Bulloch,[10] in speaking upon the acid-fast properties of the tubercle bacillus, mentioned that it was also alcohol fast, and that these properties (acid and alcohol fast) were not due to the presence of fat in the bacillus, but to a body of a waxy nature, which, when removed from the bacillus with boiling chloroform or boiling benzin, was in itself powerfully acid fast and unstainable by fat stains (Aronson). Besides wax and fat, which were present in relatively large amount, the tubercle bacillus was composed of proteids, important among which was a variety of nucleic acid described as tuberculinic acid (Ruppel) and salts, with phosphate predominating. After the removal of all proteids, wax, and fat, a substance remained which contained a considerable quantity of nitrogen, and from its reactions was probably chitin or some allied body.

In this communication the writer presents a series of experiments determining the actual resistance of the acid-fast bacilli to mineral acids and other reagents.

In the first experiments (Table No. I.) spreads were made from three-weeks-old cultures of the organisms, excepting, of course, the smegma bacillus. The spreads were dried, fixed, stained for fifteen minutes with carbol fuchsin, heating the cover-slip slightly during this time. They were next washed with water, then the reagent applied from fifteen to thirty minutes. In most of the preparations fifteen minutes was the maximum time limit, while some actually resisted the reagents forty-five minutes. The same technic was also resorted to in using anilin gentian violet, with practically the same results as those obtained with carbol fuchsin.

It will be seen that with sweet spirits of niter and glacial acetic acid (full strength) all organisms were decolorized with the exception of the bacillus of human, bovine, and avian tuberculosis.

With 20 per cent. nitric acid all were decolorized, with the exception of the bacilli of human and bovine tuberculosis and the

smegma bacillus. They all resisted 25 per cent. sulphuric acid with the exception of the grass bacillus (Korn I.) and the milch bacillus. Besides the margarin bacillus, grass bacillus (Moeller II.), and blindschleichen bacillus, they all resisted 30 per cent. sulphuric acid. With 40 per cent. sulphuric acid they were all decolorized, with the exception of the bacilli of human, bovine, and avian tuberculosis, Karlinski's bacillus, and the horse-dung bacillus. With 30 per cent. hydrochloric acid, the bacillus of fish tuberculosis, Grassberger's butter bacillus, Korn's grass bacilli Nos. I. and II. and the smegma bacillus were decolorized. With absolute alcohol only the smegma bacillus was decolorized. Twenty per cent. sulphurous acid failed to decolorize any, even after thirty minutes' application.

Tartaric acid (1 : 20) in watery solution as well as alcoholic solution of same strength failed to decolorize any of the organisms.

TABLE I.

	Resistance to.					— Decolorized by.				
Carbol fuchsin.	Sp. eth. nitrosi.	20 per ct. HNO_3.	30 per ct. HCl.	25 per ct. H_2SO_4.	30 per ct. H_2SO_4.	40 per ct. H_2SO_4.	Absolute alcohol.	Glacial acetic acid.	20 per ct. H_2SO_3.	1 : 20 tartaric acid.
Human T. B.	×	×	×	×	×			×	×	
Bovine T. B.	×	×	×	×	×			×	×	
Avian T. B.	×	—	×	×	×			×		
Piscian T. B.	—	—	×	×	×	—		—	×	
Butter B. Rabinowitsch	—	—	×	×	×	—		—	×	
Butter B. Grassberger	—	—	—	×	—	o		—		
Margarin B.	—	—	×	×	×		×		×	
Grass B. Korn I.	—	—	×	×	×		×		×	
Grass B. Korn II.	—	—	×	×	×		×		×	
Grass B. Moeller I	—	—	×	×	×		×		×	
Grass B. Moeller II	—	—	×		×	—	×		×	
Mist B.	—	—	×		×	—	×		×	
Horse-dung B.	—	—	×	×	×	×			×	
Milch B.	—	—	×			—	×		×	
Blindschleichen B.	—	—	×	×	×	—	×		×	
Karlinski's B.	—	—	×	×	×	—	×	—	×	
Smegma B.	—	—	—	×	×	—	—	—	—	

The next experiments were made by boiling in xylol spreads of the organisms. They were then stained with carbol fuchsin and afterward treated with 25 per cent. sulphuric acid; all resisted

except Korn's grass bacillus No. I., the milch bacillus, and bacillus smegmatis.

Spreads were then boiled in a 5 per cent. aqueous solution of sodium hydrate, stained as before, and treated with 25 per cent. solution of sulphuric acid, with the result that all decolorized with the exception of the bacillus of bovine and human tuberculosis. If the bacillus of human and bovine tuberculosis and the smegma bacillus are treated with sodium hydrate and then with 25 per cent. nitric acid they will be completely decolorized. If a 5 per cent. alcoholic solution of sodium hydrate is used and spreads of the human tubercle bacillus and the smegma bacillus stained with carbol fuchsin and afterward treated with 25 per cent. solution of sulphuric acid the smegma bacillus is decolorized while the human tubercle bacillus still retains the dye.

TABLE II.

× Resistance to. — Decolorized by.

	Xylol followed by 25 per ct. solution H_2SO_4.	5 per ct. aqueous solution NAOH followed by 25 per ct. H_2SO_4.	5 per ct. aqueous solution NAOH followed by 20 per ct. HNO_4.
Human tubercle B.	×	×	—
Bovine " "	×	×	—
Avian " "	×	—	—
Fish " "	×	—	—
Butter B. Rabinowitsch	×	—	—
Butter B. Grassberger	×	—	—
Margarin B.	×	—	—
Grass B. Korn I.	—	—	—
Grass B. Korn II.	×	—	—
Grass B. Moeller I.	×	—	—
Grass B. Moeller II.	×	—	—
Mist B.	×	—	—
Horse-dung B.	×	—	—
Milch B.	—	—	—
Blindschleichen B.	×	—	—
Karlinski's B.	×	—	—
Smegma B.	—	—	—

The next series of experiments were upon spreads of fresh sputum containing tubercle bacilli, spreads made from sputum preserved in Strohschein's solution for eighteen months, and spreads of smegma. These were treated in various ways, as will be seen by the appended table. The interesting point is that the

tubercle bacillus retains its acid-resisting properties for an indefinite time in a preserving solution.

TABLE III.

× Resistance to. — Decolorized by.

Spreads of fresh sputum.	Spreads of preserved sputum.	Spreads of Smegma.
1. Xylol (boiled) carbol fuchsin, 20 per ct. nitric acid. —	Xylol (boiled) carbol fuchsin, 20 per ct. nitric acid. —	Xylol (boiled) carbolic fuchsin, 20 per ct. nitric acid. —
2. Xylol (boiled) carbol fuchsin, sweet spirits of niter. ×	Xylol (boiled) carbol fuchsin, sweet spirits of niter. ×	Caustic soda (5 per ct. aqueous solution) boiled, carbol fuchsin, 20 per ct.. nitric acid. —
3. Caustic soda (5 per ct. aqueous solution) boiled, carbol fuchsin, 20 per ct. nitric acid. —	Caustic soda (5 per ct. aqueous solution) boiled, carbol fuchsin, 20 per ct. nitric acid. —	Caustic soda (5 per ct. alcoholic solution) boiled, carbol fuchsin, 20 per ct. nitric acid. —
4. Caustic soda (5 per ct. alcoholic solution) boiled, carbol fuchsin, 20 per ct. nitric acid. —	Caustic soda (5 per ct. alcoholic solution) boiled, carbol fuchsin, 20 per ct. nitric acid. —	Carbol fuchsin, 40 per ct. sulphuric acid. —
5. Carbol fuchsin, glacial acetic acid (pure). ×	Carbol fuchsin, glacial acetic acid (pure).	Carbol fuchsin, sweet spirits of niter. —
6. Caustic soda (5 per ct. aqueous solution) boiled in carbol fuchsin, glacial acetic acid (pure). —	Caustic soda (5 per ct. aqueous solution) boiled in carbol fuchsin, glacial acetic acid (pure). —	Ether (boiled) carbol fuchsin, 20 per ct. nitric acid. —
7. Carbol fuchsin, 40 per ct. solution sulphuric acid. ×	Carbol fuchsin, 40 per ct. solution sulphuric acid. ×	
8. Ether (boiled in) carbol fuchsin, 20 per ct. nitric acid. —	Ether (boiled in) carbol fuchsin, 20 per ct. nitric acid. —	
9. Carbol fuchsin, 1 : 20 tartaric acid (aqueous). ×	Carbol fuchsin, 1 : 20 tartaric acid (aqueous). ×	
10. Carbol fuchsin, 1 : 20 tartaric acid (alcoholic). ×	Carbol fuchsin, 1 : 20 tartaric acid (alcoholic.) ×	

The latter series of experiments shows how long the tubercle bacillus resists acids. The fact that numerous observers have

found acid-fast bacilli in the sputum and in the parenchyma in cases of gangrene of the lungs would lead one to suggest that these might represent dead or attenuated forms of the tubercle bacillus. Their decolorization with alcohol after the application of acid would, however, negative this view.

As some observers have shown, in young cultures of the tubercle bacillus some of the organisms decolorize with acids, the writer found the same condition in young cultures of the various acid-fast organisms studied.

In morphology some of these organisms may be taken for the human tubercle bacillus, but the majority of them were shorter, especially so in old cultures. Where a spread of milk or butter contains only one or two demonstrable acid-fast bacilli, it is then that some doubt may arise as to what organism we are dealing with.

Of course, the best and seemingly the only way in very doubtful cases to differentiate these various organisms is to make cultural as well as inoculation experiments upon animals when they can be readily told apart.

The growth of the butter, grass, and milk bacilli make their appearance in thirty-six or forty-eight hours at ordinary room temperature, while that of the tubercle bacillus requires at least ten days at body temperature.

The fact should also be borne in mind that the butter and other bacilli grow upon plain agar, while the tubercle bacillus requires blood serum or glycerin agar.

Tartaric acid, either in alcoholic or watery solution, failed to decolorize any of the organisms, though Foli claims that with this solution he was able to differentiate the "pseudotubercle" bacillus in sputum from the true tubercle bacillus.

Watery mixtures of all the bacilli mentioned were made and treated with 1 per cent. solution of osmic acid, to determine whether the fat of the organisms responded to this reagent. In all, the sediment which collected at the bottom of the tubes was turned black. In hanging-drop preparations all the organisms were of a brownish tinge, with the exception of Korn's grass bacillus No. I. and Moeller's grass bacillus No. I. Spreads were then made, fixed and stained, with carbol fuchsin, and treated

with a 25 per cent. solution of sulphuric acid. They were seen to still resist the acid.

It has been stated by Sebrazes (quoted below) that if sputum or any material containing tubercle bacilli was exposed to the action of nitric acid the organism would then not respond to a stain; in fact, lose its tingibility. Spreads of fresh sputum were made; one-half of the surface was paraffined and then placed in a 1 per cent. solution of nitric acid for eighteen hours. This left one-half of the cover exposed to the acid solution. At the end of this time the paraffin was removed with xylol and the spreads stained with carbol fuchsin, then treated with Gabbet's solution. It was seen that the bacilli stained as well as if no acid solution had been previously applied.

Sabrazes[11] has experimented upon the colorability of the bacillus of Koch. Stain used Ziehl-Neelsen. The staining is not influenced by distilled water, boiling water, anilin-water H_2O_2—twelve volumes; Lugol's solution, alcohol, ether, chloroform, xylol, benzin, acetic acid, sat. aq. sol. of boric acid, picric acid, carbolic acid, sat. alc. sol. of salicylic acid, ammonia, caustic soda, carbonate of sodium, sulphite of sodium, KI, sulphate of aluminum, sulphate of copper, chlorid of barium saturated in water, bichlorid of mercury 1 : 100 or 1 : 1000, cyanid of mercury 1 : 100 or 1 : 1000, creolin mixtures, Van Swieten's liquid, the reagents of Esbach and Fleming. The bacilli cannot be identified in sputum treated with nitric acid, HCl, H_2SO_4, 1 per cent. osmic, 1 per cent. permanganate of potassium, bichlorid of tin and nitrate of bismuth saturated in water, sulphite of ammonium, reagent of Boas, sulphomolybdic acid. The tingibility is slightly affected by chromic acid 2 per cent., formol, H_2SO_4 24 per cent. in water for two days, sat. aq. sol. of acetate of lead, nitrates of barium and silver 1 per cent., acid alcohol 2 per cent., chromate and bichromate of potassium saturated in water, alcoholic solution of phenolphthalein: the acetopicric reagents of Fehling, Kleinenberg, Tauret, Uffelman, and tincture of iodin. The ferricyanid of potassium and nitroprussiate of sodium, when brought in contact with Ziehl-Neelsen solution, cause a precipitate of crystals that resemble tubercle bacilli.

The conclusions deduced from these few experiments are that in doubtful cases, where acid-fast bacilli are encountered, a diagnosis of tubercle bacilli can be positively made by after-treatment of the stained spread with sweet spirits of niter or glacial acetic acid, as these two reagents completely decolorize other acid-fast organisms, as the grass and butter bacilli and the smegma bacillus. Inoculation experiments should always be made where only a few organisms are observed.

I wish to extend my thanks to Dr. Ravenel for the various cultures used in the experiments.

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DISCUSSION.

DR. MCFARLAND asked whether the speaker had obtained his results with one solution of carbol-fuchsin or with different solutions, as he thought there might be a possibility of obtaining varying results with different solutions.

DR. ROSENBERGER, in reply to Dr. McFarland, said that he had used different kinds of fuchsin (powdered and granulated), but that his results had been uniform. *December* 10, 1903.

Report of a Case of Brain Tumor and of a Case of Ruptured Tubal Pregnancy.

MOSES BEHREND, M.D.

I. CASE OF BRAIN TUMOR.

It will be impossible to give a full history of the cases represented by these specimens, because it would consume too much time, and especially since they will be completeiy reported at a later date.

The brief history of the case of brain tumor is as follows:

H. W., aged forty-four years; Hungarian by birth.

Previous History. Unimportant.

Family History. Entirely negative.

Present Condition. The patient was first seen on October 23, 1903, when she complained of weakness, which existed more or less for the past seven months. One week after the first visit the weakness increased, followed by a supposed attack of vertigo. This was followed by loss of power in the left arm and leg. Motion returned the next day, though somewhat weakened. In the course of six weeks these epileptiform attacks of a Jacksonian type occurred at intervals, and they were always limited to the left arm and leg. The knee-jerks were increased, station was poor, left arm was held limp by the side, the left leg was dragged in walking, characteristic of a hemiplegic. Sense of location was good; sensation to pain, touch, heat, and cold were normal. Astereognosis was probably present. This could not be definitely ascertained, as the patient was unable to grasp. In the course of a few weeks the last signs to appear were ankle clonus, and the Babinski reflex. Optic disks were normal. These signs showed that there was some organic condition present, and from the foregoing symptoms a diagnosis of brain tumor was made. There was no nausea or vomiting, but headache was a prominent symptom. Associated in this case were Drs. Mills, Sinkler, and Keen. The latter successfully removed the tumor, which was in the rolandic region, two months after the patient came under my observation. At the present time the patient is able to walk fairly well, but the arm has not recovered itself.

II. Ruptured Tubal Pregnancy.

The history of this case is full of interest. It is as follows: P. S., aged thirty-five years, American. Family history has no bearing on the case. Previous history is important, especially that relating to the menstrual function. She had five children, two of whom were born at the eighth month. Last child was born nine-

teen months ago. All the labors and pregnancies were full of complications. Since the birth of the last child she menstruated regularly up to November 11, 1903. She consulted me for this, and believing herself to be pregnant she wanted something to reinstitute this function. My answer in this case, as in all others, is that there is no drug that will help them. This usually ends the controversy. The patient was not satisfied, and took a very hot vaginal douche. Five days afterward I saw the patient for colic, which was referred to the right iliac region. A vaginal examination was made, but nothing abnormal could be outlined. A few days after this the supposed menstruation occurred. This takes us to the present history, which dates from December 14, 1903, when the rupture occurred. The patient was preparing breakfast at 6.30 A.M., when she was suddenly seized with pain in the right iliac region, which completely disabled her. Upon reaching the patient, an hour later, she was in a very grave condition. She complained of pain in the right iliac region, which was fixed. Her condition was one of extreme shock. She was ghastly, pulse thready and rapid, and an intense look of anguish, with the fear of impending death, made a picture hard to forget. The abdomen was slightly distended, and palpation caused pain.

Seeing the necessity of an early operation, Dr. William Teller was called in consultation. He rendered most valuable aid throughout her entire illness.

After an examination we decided that a rupture either of the appendix or Fallopian tube had occurred, and that an immediate operation was imperative.

General anesthesia and her removal from home were entirely out of the question with the patient in a condition of profound collapse. About five hours after the rupture we operated without anesthesia. Upon opening the abdomen liquid and clotted blood gushed out. This immediately settled the diagnosis.

Words can hardly describe our feelings upon seeing such an enormous volume of blood flowing from the abdomen. Naturally, from the symptoms, we ligated the right side first, but still the blood poured out. We then ligated the left tube, where a very

tiny rupture was found. Both tubes were removed, the whole of the right ovary and part of the left. The operation lasted twenty-three minutes, after which the patient rested well.

The remarkable nerve and physical endurance displayed by the patient account for the result we obtained, notwithstanding the fact that we had a badly infected wound. This was expected, on account of the conditions under which the operation was performed, in a room about five by nine feet. In addition to the infected wound, septicemia followed, and a large pelvic mass was found, which proved to be an organized blood-clot which had undergone degeneration. For this we operated twice, once two weeks after the first operation, and again without anesthesia. This only gave temporary relief. One week after this operation we decided to open Douglas' sac again under general anesthesia. This was accordingly done, and the enormous pelvic mass was broken up, which extended to the abdominal wound and all around the uterus. The mass just described was as large as a cocoanut. For a few days after this operation we were very dubious as to the ultimate recovery of our patient. But her magnificent physical endurance came to our rescue again, and we are glad to report this evening that the patient is entirely out of danger. Only a few days ago she was attacked with a mild form of erysipelas of the face. This subsided in three days. The appearance of this affection at this time reminded us that we were dealing with a streptococcic infection.

January 4, 1904.

Proceedings

of the

Pathological Society of Philadelphia.

FEBRUARY, 1904. NEW SERIES, VOL. VII., NO. 2.

TABLE OF CONTENTS.

SAILER, A Review of the Recent Literature upon the Pathology of the Liver.—FARR, A Case of Splenomegaly, with Cirrhosis of the Liver.—STAHL, Pancreatic Hemorrhage; Death; Autopsy,—Report of the Committee on Morbid Growths Concerning Dr. Stahl's Specimen.—MCFARLAND, A Case of Xanthoma.—WEISENBURG, Uremic Hemiplegia, with Changes in the Nerve Cells of the Brain and Cord, and Recent Primary Degeneration of the Central Motor Tract.

A Review of the Recent Literature upon the Pathology of the Liver.*

JOSEPH SAILER, M.D.

I have not attempted to cover more than the recent literature upon the pathology of the liver, and this has been so considerable that it has been impossible to cite even a fairly large proportion of the articles. I have merely endeavored to indicate the more important lines of research, and to discuss the actual progress made.

It cannot be said that any substantial contribution has been made in the year 1903. The primary carcinoma of the liver has been studied; necroses have been more carefully investigated; ingenious studies, designed to elucidate the subject of hepatic regeneration, have been made; and the various forms of infections have been described. Otherwise, the papers have been the reports of isolated cases, often of clinical rather than pathologic interest.

ANATOMY. The bile-duct[1] before entering the duodenum passed through the head of the pancreas in 95 per cent. of 58 cases. It united with the duct of Wirsung in only 1 per cent. or 2 per cent. of the cases.

* Read by invitation.

The liver cells appear to have a complicated anatomy.[2] Not only do they contain bile capillaries lined with squamous epithelium, but there is reason to believe that spaces exist which communicate with the blood capillaries. It is possible that the granules that can be seen in the cell correspond in a way to organs of the cell, and fulfill various secretory and nutritive functions. The intracellular spaces may also serve to explain certain pathologic processes in the cell, particularly vacuolization.

A new method of staining the biliary capillaries[3] based upon Weigert's neuroglia stain shows that their arrangement in human beings is more complicated than in the lower animals, and that intracellular bile channels exist. Perivascular spaces exist also, probably lymphatic, and when obstructive jaundice occurs the capillaries rupture into them. If the intracellular capillaries rupture, the cells containing them become necrotic.[4] The method does not suffice to determine the nature of all forms of jaundice; it shows, however, that there is no common histologic change, such as alteration in the cells. In cirrhosis the jaundice is apparently due to the strangulation of the capillaries; in phosphorus poisoning and in passive congestion, to bile thrombi with consecutive rupture of the capillaries. Further studies with the method[5] show that the biliary capillaries form a network of anastomoses with no blind ends. In obstructive jaundice in rabbits there is first a constriction of the capillaries, due probably to functional disturbance of the liver cell and cessation of the secretion of bile, and later, when the cell has recovered, distention and rupture. Apparently the same phenomena occur in human livers. Necroses do not occur unless infection has taken place. The purely mechanic theory of jaundice has not been universally accepted. It has been claimed upon the basis of clinical studies[7] that jaundice does not occur unless there has been infection. Gilbert and Lereboullet[8] describe a familiar type of cholemia which may be associated with migraine, vomiting of or the passage of pure bile, and with pains in the region of the liver or spleen. The mechanism is not clear, but there appear to be recurrent attacks of cholangitis.

A few congenital anomalies have been reported, among them two cases[9] in which the left lobe was represented only by a small mass of fibrous connective tissue. In one the spigelian lobe was enor-

mously hypertrophied; in the other it was reduced to the size of a hazelnut. In both cases the right lobe was greatly enlarged, but in the first it showed also some atrophic areas. The hepatic vessels divided normally, but both branches supplied the right lobe. Both gall-bladders were normal.

Physiology. The effect of disturbance of the hepatic function upon the other tissues of the body has received some attention. The separation of the liver from the general circulation of the blood[10] does not appear to reduce the freezing point of the blood. Excessive secretion of bile, 2000 c.c. per day, causes a diminution in the secretion of urine and uremic vomiting.[11] In states of anemia and hunger the liver seems to have the faculty of attracting to itself the iron absorbed from the duodenum and retaining it in loose combination.[12]

The subject of the bactericidal or bacteriolytic action of the liver has been studied. There appears to be reason to believe that the liver glycogen retards the growth of microorganisms, and, by rendering the culture medium acid, may actually kill them. The liver substance of rabbits has no bactericidal action upon the colon bacillus.[13]

Degeneration and Inflammation. The results of the experimental inoculation of mice with the minimum lethal dose of hog-cholera bacillus gives rise to exquisite focal necroses in the liver.[14] These necroses are apparently always due to vascular obstruction, either as a result of thrombosis with hyaline material, or to the aggregation of large mononuclear cells which are probably phagocytic in nature. These appear within twenty-four hours after the injection; are most numerous near the capsule of the liver, or the walls of the veins; and show degenerative changes whose commencement is usually indicated by an alteration in the nucleus. They are probably identical with the large mononuclear leukocytes. They form thrombi as a result of being fastened together by fibrin. Subsequently they liquefy and disappear, the fibrin taking their place. In the neighborhood of these clumps necrosis occurs in the liver cells. This necrosis rarely affects more than part of a lobule. The hyaline thrombi affect larger vessels, and, as a result, there is more extensive necrosis of the liver, the cells first staining deeply with eosin, and then losing their power to take the stain.

These thrombi are produced by the coalescence and degeneration of the blood corpuscles. It could not be shown that the bacteria had anything to do with these thrombi. They were not present in the livers of animals killed, but only in those that were allowed to die of the infection.

There is some dispute regarding the situation of necrosis of the liver when obstruction occurs to the outflow of bile. In an instance [15] in which obstruction was produced by a tumor at the junction of the cystic and hepatic ducts, it was situated at the periphery of the lobule. Parenchymatous degeneration occurs in cases of hemorrhagic pancreatitis. [16] It seems likely that the infection of the pancreas occurs before that of the liver, but microorganisms are usually found in the latter organ.

Acute yellow atrophy has been the subject of some interesting speculations. [17] Admitting the varying etiology, either infectious, toxic, or other, the unity of the resulting changes indicates a common process. This may be autodigestion of the liver cells as a result of profound changes in their physiologic activity. In the case reported the swelling of the mesenteric lymph glands was evidence of an infectious process. The liver gave evidence of cirrhosis, although the patient was only a child.

But little has been added to the subject of ordinary cirrhosis. Some unusual forms, however, have been described. One [18] in which there was a deposit of an enormous amount of ochre-colored pigment in the liver and multiple liver abscesses. Another, in which the liver was greatly enlarged, cirrhotic, and there was pigmentary infiltration not only of it, but of all the other organs. [19] The suprarenal capsules were tuberculous and the patient had diabetes. In a somewhat similar case [20] there was cirrhosis of the liver and pancreas, diabetes, and a deposition in the various organs of a brownish pigment that gave the reaction for iron. Involvement of the pancreas is not rare; in a series of eight cases of cirrhosis of the liver a histologic study of the pancreas showed the presence of changes not unlike those found in the liver.[21]

Some of the complications of cirrhosis of the liver have been the theme of speculation. There appears to be a general dilatation in the arterial system,[21a] especially of the smallest arteries, which may rupture and give rise to serious hemorrhages, particularly

from the mucous membranes. Therefore, all the hemorrhagic manifestations of cirrhosis are not the result of portal congestion.

The studies upon the circulation of the liver indicate that various disturbances may produce conditions somewhat simulating cirrhosis. If the portal veins in a cat's liver are tied,[22] there is first disappearance of fat from the affected lobe, and then hyperplasia of connective tissue with subsequent retraction. The portions of the liver not involved in the circulatory disturbance undergo compensatory hypertrophy. If an artery leading to a lobe is ligated at the same time that the branch of the portal vein is ligated, rapid necrosis occurs, invariably associated with bacterial thrombi in the vessels. It seems difficult to understand how these thrombi occur, but presumably the bacteria pass from the intestinal tract to the liver along the portal vein, and are then destroyed by the parenchyma of the liver cells. Emphysema of the liver (Schaumleber) was observed. In the same series of investigations the hepatic artery was ligated five times, in each giving rise to necrosis of the whole liver, with death inside of forty-eight hours. The cirrhosis of the liver which occurs in Banti's disease is not so clearly understood. If this disease can be separated from infectious processes, such as late hereditary syphilis, chronic malaria, and also from splenic anemia, it could be regarded as independent.[23] There appears to be no doubt, however, that the splenomegaly in this group of cases is primary, and that the cirrhosis of the liver is secondary. Some investigators[24] believe that there is no essential difference between ordinary so-called splenic anemia and Banti's disease. It appears that many cases observed in the northern part of Europe are late hereditary syphilis. (The peculiar histologic changes in the spleen, so carefully described by Banti, are not sufficiently considered in making the differential diagnosis in these cases.)

In Hungary a curious disease has been observed, apparently not found elsewhere,[25] the chief characteristic of which is sclerosis of the portal vein. The clinical course is variable; in one case thirteen weeks, in another about seventeen months. The symptoms are ascites, edema, dyspnea, and in one case hemorrhage from the intestines. At the autopsy the wall of the portal vein was found thickened and contained calcareous plates. The lumen was dimin-

ished and there was mural thrombosis. In the liver the changes consisted in a proliferation in the interacinal connective tissue, pronounced at the periphery and absent at the center of the lobes. The liver cells were in general atrophied, with a few localized foci of regeneration. The walls of all the branches of the portal veins were thickened. There were also some changes in the other veins of the abdominal cavity. A case with somewhat similar clinical symptoms—that is, ascites, gradual exhaustion, and death—was found to be due to obliteration of the hepatic vein at its entrance into the inferior cava.[26] Mere passive congestion of the liver is apparently not capable of causing true cirrhosis.[27] The granular appearance of the surface of the liver in these cases is probably due to hypertrophy of the parenchyma and focal atrophies. Therefore, when ascites occurs as a permanent symptom of chronic cardiac disease, it must not be regarded as a result of the passive congestion.

A variety of causes may produce abscess of the liver. Stones, or injury,[28] or parasites, a case due to infection with the distomum sineuse, acquired in China, having been observed in America.[29]

A case of multiple abscess of the liver has been recorded[30] in which an anaerobic streptococcus and a bacillus were found growing symbiotically and were regarded as the cause.

In a series of twenty cases, studied postmortem,[31] it could be determined that the infection travelled along the bile-ducts seven times; along the portal vein eight times; along the hepatic artery three times; and twice there was direct transmission from a suppurating carcinoma. In sixteen cases the microorganism was determined, seven times the colon bacillus being found; twice the Staphylococcus albus; once the Staphylococcus aureus; once the streptococcus, and once Friedländer's bacillus. Some experiments showed that pus infected with the staphylococcus resisted invasion by the colon bacillus, but that pus previously sterile did not. There is reason to believe, therefore, that although postmortem invasion may occur, it is of relatively subordinate importance, and that the bacteriologic examination of the liver abscesses after death is not less valuable than those discovered at operation, although in the latter case it appears, from Giordano's investigations, that sterile abscesses are more common than any other

form. The twenty cases were found in 4907 autopsies, a proportion of 1 in 245. Statistics obtained from more southerly regions show a higher proportion than this. Although there were numerous cases of injuries to the skull with secondary hemorrhage into the liver, no case of liver abscess appeared to be due to this cause. The commonest general causes were biliary calculus, causing infection along the bile-ducts; carcinoma, giving rise to general infectious processes: general sepsis; and hemorrhagic enteritis.

A series of four cases indicates the variable etiology of this condition. One was due to gallstone, a second probably to the same cause, especially as a biliary cirrhosis was also present, and a third to traumatism. In the fourth case the etiology was not determined.[32]

A few cases have been reported of emphysema of the liver: one ascribed to the Bacillus perfringens;[33] three others in which the gas was formed in the bile-ducts due to the colon bacterium and the Bacillus lactis aerogenes.[34]

Streptococcic infection and erysipelas appear to have very slight effect upon the liver.[34a]

In smallpox the liver is usually enlarged, pale yellow in color, and softened. These macroscopic changes are shown microscopically to be due to fatty infiltration of the cells, affecting first the peripheral and later the central portions of the lobules. Chemically examined the liver shows a larger proportion of fat and a smaller proportion of water after the fifth day of the disease.[34b]

In hemorrhagic pancreatitis the liver shows parenchymatous hepatitis, and there is necrosis of the abdominal fat. This is probably secondary to the disease of the pancreas.[34c]

In a case of diabetes associated with lipemia[34d] there were observed delicate fibers surrounding the capillaries in the form of a network. These were only seen in preparations stained by Van Giesen's method. They were also found in the tissues from three other cases of diabetes. Apparently they have not previously been described.

Tumors. Of the tumors of the liver those which have excited the greatest amount of interest are the primary carcinomas. A number have been reported as such without any particular reference as to

whether they arose from the bile-ducts or the liver substance.[31e] A number of authors, however, have tried to determine their origin in particular instances. Not infrequently there can be no doubt, from the character of the primary growth and the existence of metastases containing cylindric cells in the lymph glands, that the epithelium of the gall-bladder is the primary seat.[35] Other cases, however, occur in which the arrangement of the cells resembles that of the parenchyma of the liver, and these have usually been considered true primary carcinomas. A careful study of such a tumor, however, showed that in the center it resembled the structure of the bile-duct carcinoma: toward the periphery, however, the cells were polygonal and grouped in masses or columns. In the metastases the polygonal cells predominated. As, however, all the stages of transition between the alveolar arrangement of the cylindric cells and the solid columns of polyhedral cells could be observed, it was concluded that in these cases also the tumor cells were primarily derived from the epithelium of the bile-ducts. The invariable association of cirrhosis with this process is noted. A series of seven cases[36] carefully studied histologically led also to the conclusion that these primary carcinomas are derived from the bile-ducts. The cirrhosis was regarded in all cases as strictly secondary. Another author,[37] however, concludes that the cirrhosis is primary and the carcinoma secondary. Still another author[38] believes that although the cirrhosis may precede the carcinoma, it is incapable of causing it, and that the two processes are necessarily independent, although they may coexist. Further proof of the biliary origin of the carcinoma is found in a case in which, although the cells of the tumor were of the polyhedral type, they contained bile pigment. Unfortunately, in this case there was chronic jaundice due to gallstones, so that there is some doubt regarding the source of the pigment.[39] Occasionally the cylindric-cell epithelioma arising from the gall-ducts may develop to an enormous size. In one such case,[40] occurring in a woman of fifty years, who had had gallstone colic, large metastases were found in the substance of the liver.

The literature of the whole subject has been carefully studied,[41] and the following statistics obtained: Of the 52 recorded cases, 37 have been studied anatomically and pathologically. In 46 cases

in which the sex is given, 30 occurred in men and 16 in women. In one-fifth of the cases stones were present. The patients were usually over sixty years of age. The commonest situation was the ductus choledochus. Of 22 cases, it was at the junction of the hepatic and cystic ducts in 15 cases. In only 1 case was there a carcinoma of the cystic duct; in 7 cases of the hepatic duct. The primary tumor is usually smaller than a pigeon's egg. Sometimes it is annular; rarely it invades the lumen of the gall-duct. As a result the bile-ducts are not infrequently patulous. In only 10 cases had metastases occurred; in all to the liver. Occasionally the lymph glands in the gastrohepatic ligament were swollen. Twenty-five of thirty-four carefully studied cases were of the cylindric-cell type. In the others the nature of the epithelium is not precisely stated. Clinically, it is noted that if the tumor is below the junction of the two ducts the gall-bladder is distended. If in the hepatic duct, above, it is usually contracted, unless there is a second stricture lower down. Infection of the bile-ducts is exceedingly rare. In three cases there was purulent cholecystitis; in one, a gangrenous inflammation of the wall of the gall-bladder with perforation; and in one a large abscess of the liver. Two cases had general sepsis. In 25 of 52 cases the liver was enlarged; twenty-three times as a result of stagnation of the bile; twice on account of carcinomatous metastasis. In an additional case of this type the tumor was found 2 cm. from the diverticulum of Vater, at the junction of the hepatic and cystic ducts. It consisted of fine papillæ into the lumen of the duct, and strings of epithelial cells penetrating the stroma of the wall. A diagnosis was made of carcinoma papilliferum annulare hæmatodes.[15] In this case there was no metastasis; the gall-bladder was distended and had ruptured without ulceration; there was necrosis of the walls of the liver and pancreas, and hemorrhage had occurred by diapedesis into the biliary system.

Secondary tumors are only interesting when the primary growth cannot be found. In one such instance[13] it was assumed to have existed in the intestinal tract, where it was overlooked during operation. A somewhat similar case[41] is recorded as a primary tumor of the liver.

Among the other tumors that have been reported the most

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interesting is the large lymphangioma removed by operation from the liver of a boy five years of age. A palpable tumor had existed for three years. It had the usual histologic structure, including the formation of multiple cysts.[15] The solitary adenoma of the liver[16] is benign, and probably due to congenital disturbance of the tissues. Two cases of primary sarcoma,[17] occurring in children of three and eleven years of age, have also been reported.

Cysts have been recorded in a variety of cases. The study of eighteen cases—one original and seventeen derived from the literature—indicates that the nonparasitic cysts are of very various nature. The congenital cysts are usually lined with ciliated epithelium or contain mucus, or are true dermoid cysts. The cystadenoma is due to the proliferation of the gall-ducts and subsequent dilatation of these newly formed channels forming, at first multilocular and subsequently, by the obliteration of the septa, unilocular cysts. The majority of so-called biliary cysts are of this nature. Occasionally, as in the original case reported, congenital atresia of the ductus choledochus gives rise to true retention biliary cysts. Of course, these are only found in newborn children, because the lesion is incompatible with extrauterine life.[18]

Of the parasitic cysts the interesting observation has been made[49] that active regeneration, compensatory in type, may occur in the liver. Attention has also been called to the similarity between the echinococcus cyst of the liver[50] and malignant tumors. They affect chiefly the right lobe, may give rise to metastases, as, for example, to the gall-bladder, the lung, brain, kidneys, and peritoneum, and may grow into and proliferate in the blood-vessels.

Gallstones. Gallstones, in view of their increasing surgical importance, have attracted more and more attention from pathologists. Among the curious lesions produced are obstruction of the intestine, which was produced in one case by a stone weighing 10 gm.,[51] and in another by one weighing 15 gm.[52]

The bacteriology of gallstone disease has attracted a good deal of attention. In one series of forty-six cases in which the bile obtained at operation for gallstone disease was examined bacteri-

ologically it was found sterile ten times; contained the Bacterium coli twenty-three times; streptococci, twice; staphylococci, four times; very fine, rod-shaped bacteria, once; and mixed infection, five times. Infection appeared in all cases to come from the intestinal tract, and to be due either to stagnation of the bile as a result of obstruction, or as a result of diminished motility on the part of the gall-bladder.[55]

An additional factor which may also be concerned in the causation of gallstone is floating kidney. It is supposed to act by compressing the gall-ducts, or by pulling upon the hepatoduodenal ligament and causing a kinking in the gall-ducts, thus producing stagnation of the bile and formation of the gallstones, in the same way that it has been supposed that jaundice can be produced.[56]

The relation of the gallstones to the wall of the gall-bladder is various.[57] They may be free or fixed, either by incarceration, by adhesion to the wall of the gall-bladder, or by being wholly or partially surrounded by a pocket in the wall of the gall-bladder. The latter changes are produced by ulceration and cicatrization of the wall.

In a gall-bladder with numerous stones[58] discovered in a patient suffering from insanity and general tuberculosis, tuberculous infection of the wall was discovered. It appears to have been produced by transmission along the blood channels.

In subacute and chronic cholecystitis due to the presence of stones there may be either membrane formation, or, more commonly, hypertrophy of the mucous membrane with preservation of the cylindric epithelium.[59]

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A Case of Splenomegaly, with Cirrhosis of the Liver.

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Under the above name Banti described some years since (*Ziegler's Beiträge*, Bd. xxiv.) a series of cases characterized by enlargement of the spleen, cirrhosis of the liver, ascites, anemia, and a tendency to hemorrhage from the stomach. In his cases the usual etiologic factors in the production of cirrhosis of the liver or enlarged spleen were absent. Osler, who has recently written at length upon the subject, and who has reported a considerable number of cases, includes Banti's disease as the terminal stage of a clinical entity which he denominates chronic splenic anemia (*American Journal of the Medical Sciences*, November, 1902). Wentworth (*Boston Medical and Surgical Journal*, 1901) and Marchand (*Münch. med. Woch.*, 1902, No. 11) doubt the existence of any such disease or diseases, and are inclined to regard the reported cases as atypical examples of common affections, which bear only

a superficial resemblance to each other. Since the above-mentioned contributions to the subject appeared, numerous articles, with reports of more or less authentic cases, have been published, so that there is little to be gained by further controversy, and sufficient new material has not yet accumulated to render a new collection and sifting of cases necessary. Reports of carefully observed cases, particularly when the clinical findings are confirmed by autopsy, are, however, always of value, so that I need not apologize for the following rather detailed history. I saw the patient first in the wards of the Methodist Hospital, through the kindness of Drs. Hollopeter, Holmes, and Westcott, under whose care he successively passed, and later in the dispensary and at his home. He was under observation for a period of nine months, from April, 1902, to January, 1903, for the first two or three of which he was in the hospital. For valuable notes and aid at the autopsy I am indebted to the Resident Physician, Dr. Shoemaker.

Arthur W. was admitted to the hospital ward on April 14, 1902, on account of a profuse hemorrhage from the stomach which had occurred the previous evening. He had had an attack of epistaxis a few days before, and his family had noted for some months that he was becoming more and more sallow in color; nevertheless, up to this time he had not considered himself in any sense a sick man.

The family history was negative, there being no history of tuberculosis, cancer, syphilis, or of any affection similar to that from which the patient suffered. A sister was said to have died of hydrophobia (?). The patient was jaundiced for a short time after birth, but this did not persist. During infancy and childhood he was sickly, but he escaped all the serious infectious fevers. From the age of twelve years he was subject to frequent attacks of nose-bleed, but during the two years previous to the onset of his final illness he had been exempt from this trouble. For many years he lived in Chester, in a malarious locality, but, though the other members of the family had distinct malarial paroxysms, he did not, unless a brief illness, accompanied by diarrhea and chills, which was diagnosed as typhoid, was of that character. Two years ago, after coming to Philadelphia, he had a malarial attack of short duration. For ten years he had an abnormal enlarge-

ment of the abdomen, which became more noticeable about six months before his admission. His work as a beamer necessitated very heavy lifting, and he was in addition accustomed to overexert himself for amusement by bursting straps and ropes which he had fastened about his abdomen. He was a "teetotaler," smoked in moderation, and had never had any venereal disease.

At the time of his first admission the ward notes state that he was pale, but well nourished; the area of the heart dulness was not increased, but the apex was displaced upward; the abdomen was distended and tympanitic above, with movable dulness in the flanks; the left hypochondriac region was prominent, and on deep palpation or by ballottement a firm, smooth, movable, oval mass was felt, which on percussion gave a dull note continuous with that of the spleen. The temperature was irregular, gradually rising and, then after two weeks falling by lysis. The maximum temperature was 102°, the pulse was moderately accelerated and the respiration normal. The Widal reaction was negative, malarial parasites were absent, and the relative proportions of the various types of leukocytes did not deviate from the normal. On the other hand a few normoblasts were seen, and there was a moderate reduction of the number of red blood cells, and in the hemoglobin percentage. The urine from time to time showed a faint trace of albumin, but no casts were seen.

Owing to the persistence of the ascites, with its accompanying gaseous distention, to the recurrence of the hemorrhages (epistaxis, hematemesis, and melena) and to the uncertainty of the diagnosis, operation was undertaken on May 20th by Dr. E. E. Holmes. Previous to operation the possibility of sarcoma or tuberculosis was entertained. A small incision was made midway between the symphysis pubis and the umbilicus and nearly three liters of fluid removed. The mass, which now retreated upward, was with difficulty identified as the spleen. The liver was thought to be diminished in size, since it was quite out of reach. As a result of the operation there was for the time complete symptomatic relief, nor did the ascites recur for more than six months. Though omental adhesions did occur, as the autopsy showed, they were, in Dr. Holmes' opinion, too limited to have played any essential part in this fortunate result.

After leaving the wards in the latter part of June, the patient was able to continue light work in the mill until the middle of November, though he occasionally reported to the dispensary, and on one occasion late in September was again temporarily admitted on account of an attack of hematemesis. The symptoms of which he usually complained were dizziness, shortness of breath, epigastric pain, nausea or vomiting, flatulence, and diarrhea. They were always promptly relieved by hematinics and small doses of Epsom salts. Careful physical examinations made from time to time corresponded closely with previous findings and with the more detailed account given later; the important points were the continued presence of a greatly enlarged spleen, the absence of ascites, the narrow area of liver dulness, and a functional heart murmur.

On November 16th and 17th he had ten or more hemorrhages from the stomach, some of them measuring as much as a quart. Nausea and retching were absent. He presented the usual symptoms of acute anemia, rapid pulse, slow sighing respiration, extreme pallor, flashes of light before the eyes, vertigo, roaring in the ears, coldness of the extremities, with restlessness and at times mild delirium. Thirst was absent. A few days later there was a repetition of the hemorrhages, but of less severity. He recovered his strength slowly after this, but was never able to leave his bed, for, though hematemesis did not recur for six weeks, ascites began to develop, with associated abdominal pain and gaseous distention. In January epistaxis, hematemesis, and melena once more dominated the scene. A furious succession of hemorrhages caused his death on January 26, 1903. At this time he had, in addition to the symptoms noted above, intense backache and agonizing cramps in the limbs. During these last months his temperature varied between 98° and 100°, and his pulse between 90 and 120. Moderate looseness of the bowels was present as a rule. Albuminuria was only once observed.

The blood examinations made on various occasions during his illness are here shown in tabular form:

Date.	Red blood cells.	Leukocytes.	Hemoglobin.	Polymorphonuclear cells.	Large mononuclear cells	Lymphocytes.	Eosinophiles.	Normoblasts.	Remarks.
1902			Per ct.	Per ct.	Per ct.	Per ct.	Per ct		
April ?	3,200,000	4175	60	.....	"normal."		.....	Few	Hemorrhage a few weeks before.
July 7?	4,150,000	3200	55–60	56	2	37	5	Few	
Sept. 27	4,000,000	5400	40[1]	.....	.....	.....	.....	.....	After hemorrhage
Nov. 23	1,697,500	6355	10–20	.....	.....	.....	.....	.....	After hemorrhage
Dec. 4	"Similar,"	.....	.....	73	1	25	1	Very numerous	Moderate paleness of red blood cells in this and following count.
1903									
Jan. 23	1,750,000	1568	20	56	4	38	2	Numerous	After severe hemorrhage.

The physical examination, with the changes which occurred during the last two or three months, follows: The patient was not much emaciated, but he was extremely pale, with a lemon hue. The sclerae were white, with a bluish cast, and never showed the slightest indication of jaundice. There was no edema nor any pigmentation of the skin. A heaving impulse was seen, at first just outside the nipple in the fourth interspace, later farther to the left. There was also marked pulsation in the vessels of the neck. Litten's sign was easily made out early in the case, but later, owing to pleural effusion, was not observable. The abdomen from the first was large, flattened in the middle, and prominent in the flanks, this form becoming more pronounced when the ascites recurred. At times there was marked distention in the epigastric region. Projecting from beneath the costal border on the left a tumor was plainly visible, slightly elevated, and apparently about the size of the hand. Its free border was rounded in outline, and on mensuration was found to extend four inches beyond the border of the ribs, reaching within two inches of the navel. These measurements did not increase between September and January. No notch was to be detected by palpation. As ascites developed, a plain fluctuation wave in the flanks was obtained. Abdominal tenderness was slight or absent.

[1] Hemoglobin estimated by Fleischl instrument. In the other examinations the Talqvist scale was used.

The area of heart dulness was increased a finger's breadth, and later more, toward the left, while the dulness above began at the second rib, the apex being correspondingly found in the fourth interspace. The liver dulness extended only from the fifth to the lower border of the sixth rib, though later this was obscured as a result of the pleural effusion, which caused a movable dulness in the right as well as the left axilla. On auscultation a loud systolic murmur was heard over the whole precordia, and, in fact, over the whole chest, as well as in all the great vessels (carotids, femorals, etc.). The murmur was harsher and more intense at the pulmonary area. At the apex there was also a rumbling presystolic murmur, with an accompanying thrill (?).

The postmortem examination was begun twelve hours after death. The body was that of a well-developed young man, of probably 140 pounds in weight, and about 5 feet 10 inches in height. Postmortem rigidity was fairly well marked, but lividity of the dependent parts was absent. There was intense pallor of the skin, which had, moreover, a yellowish tinge. Slight wasting of the upper part of the body was noted. The abdomen was distended with fluid and flattened, while midway between the umbilicus and pubis an operation scar, abont an inch in length and considerably stretched, was observed. On making the incision the subcutaneous tissues, fat, and muscles were bloodless. The great omentum was firmly adherent at the site of the operation incision over an area one inch square; it was of an extremely pale, light-yellow color. The abdominal cavity contained about six liters of clear, watery fluid. The lower bowel contained hard masses, but the intestines otherwise, on external examination, appeared normal. The appendix was long, but not inflamed. The spleen projected but slightly below the costal border, partly because its longest diameter extended more or less transversely and partly because it was shrunken as the result of the profuse hemorrhages just preceding his death. The notch was on the upper border, beneath the costal margin, and was hence inaccessible to palpation. The length was 22.5 cm., the width 12.5 cm., the thickness 7.5 cm., and the weight 800 grams. The capsule was thickened and wrinkled. On incision the pulp was bloodless and not at all friable. The liver presented a very hard, granular,

hob-nailed surface, of a decidedly yellow hue. The organ was so tilted that the thin anterior border alone came in contact with the thoracic wall. The left lobe was nearly normal in size, while the right lobe appeared only slightly larger, being markedly contracted. On incision it was firm and of a yellowish color. Its weight was 1375 grams. The gall-bladder was distended to the size of a duck's egg, with a brownish-green fluid mingled with mucus. There were no stones. The cystic duct was obliterated and there were adhesions about the gall-bladder, which had no doubt contributed to this result. The common bile-duct was patulous.

The kidneys were on incision extremely pale (anemic), and the capsules were slightly adherent; the left kidney was moderately enlarged; the suprarenals were apparently normal; the pancreas seemed to be somewhat firmer than normal. The stomach was normal in size (not dilated!); on incision it was found to contain clots, but there were no ulcers nor erosions; the mucous membrane was extremely pale, thin, and atrophic, and covered with adherent mucus. The esophagus in the last two inches above the cardia showed a varicose condition of the longitudinal veins, which was very marked indeed. Two small slit-like openings capped with clots were found in these veins. These ruptured veins were undoubtedly the source of the hemorrhages. The right pleura contained a moderate effusion; there was less in the left; there were no pleuritic adhesions; the lungs crepitated normally throughout except posteriorly, where a hypostatic congestion existed; there were no active nor healed tubercular lesions. The pericardium was normal, and the heart slightly, if at all, enlarged. About 100 c.c. of fluid blood were found in the right auricle and venæ cavæ; aside from this, all the organs and tissues were absolutely bloodless. The left ventricle was firm and the muscle was thick; the right ventricle was dilated and its muscular wall thin and flabby; the heart muscle was very pale and yellowish in color; there were no valvular lesions whatever nor any insufficiency of the mitral, as far as could be observed.[1]

Histologic examination of the spleen showed thickening of the capsule and trabeculæ and of the connective-tissue framework

[1] The liver, spleen, and lower portion of the esophagus were preserved and exhibited at the meeting.

generally. There was marked sclerosis of the Malpighian corpuscles, especially in the vicinity of the artery. There was no increase in pigment nor amyloid change.

The capsule of the liver was also thickened, and extensive interlobular fibrosis was noted, especially near the surface of the organ. Many lobules were completely surrounded by heavy bands of connective tissue, and others had been entirely replaced by this substance. The connective-tissue bands were very rich in cells, while here and there were aggregations of round cells. In other places there was a finer intralobular fibrosis. The bile-capillaries appeared to be increased in number to some degree. The hepatic veins were, like most of the bloodvessels, quite empty. The parenchyma showed moderate fatty infiltration. The sections from the mucous membrane of the stomach exhibited considerable connective tissue rich in cells between the tubules, which, moreover, were diminished in number and incompletely clothed with epithelium, the latter, possibly, an artefact. The pancreas appeared normal. One kidney (the left) showed a marked increase of connective tissue between the tubules, while several of the Malpighian bodies were converted into fibrous nodules. The cells lining the tubules were well preserved, but the lumina contained an exudate of some sort. Sections from the opposite kidney showed very little change. The heart muscle was also normal in appearance.

In conclusion it may again be stated that this case presented all the leading symptoms of the disease described by Banti, and in addition gave a history which indicated the protracted existence of an enlarged spleen ("Chronic Splenic Anemia"). As in Banti's cases, the etiology was obscure, overexertion, malaria (?), and typhoid (?) having been possible factors. Perhaps the latter disease may have been the cause of the latent affection of the gall-bladder and duct. Of the symptoms, the most remarkable was the series of hemorrhages extending over nine months and eventually causing death. He vomited blood at least twenty-five times in quantities of half a pint to a quart or more, so that it is not surprising that normoblasts were found, though Banti says they never occur. Osler (loc. cit.) and Marchand (loc. cit.), however, mention their presence under these circumstances.

June 11, 1903.

Pancreatic Hemorrhage; Death; Autopsy.

B. FRANKLIN STAHL, M.D.

Patrick McD., aged forty-one years, white, born in Ireland, occupation waiter, was admitted to the St. Agnes' Hospital, April 25, 1903.

Family history, negative; *personal history* was as follows: Had the ordinary diseases of childhood; never was a robust man. Had rheumatism three years ago. Uses alcohol freely and tobacco moderately. Has been habitually constipated. Has been complaining for the past seven weeks.

The present trouble began with pain in the abdomen, on the right side, which then spread all over the abdomen and into the chest; pain worse on the right side. These attacks occurred every day. Pains were not severe enough to cause fainting or vomiting. Five days ago became jaundiced. He has had one attack of vomiting. Bowels constipated. No appetite; bad taste in mouth.

Examination of the Patient. Skin yellow and soft; abdomen tympanitic; veins very prominent. Tenderness on percussion at costal margin in right mammary line; laterally in midaxillary line at tenth rib; in midsternal line at tip of ensiform. Abdominal walls too rigid to permit palpation of edge of liver. Skin somewhat edematous in upper epigastrium. Heart not enlarged. Relation of heart sounds good at mitral and aortic areas. Respiratory murmur clear. Pulmonary resonance good. Tongue thickly coated.

April 29th. Had much pain at base of left chest during the night. Respiratory movement causes pain. Considerable cough.

May 1st. Pain in back is severe. Urination frequent. Slept very little.

4th. Has much pain below ribs on right side. Fluctuating tumor easily palpable at this point. Pain shoots to the right shoulder.

5th. Liver extends to within one and a half inches of the anterior superior spinous process of the ilium, and has a vertical

diameter of eight inches. Jaundice and tympany have increased. There is a circumscribed tympanitic area which extends from the ensiform to the umbilicus, and appears to be due to dilatation of the stomach.

9th. The swelling over the stomach has disappeared; there is now a pyriform swelling corresponding to the position of the gall-bladder, which gives a dull note on deep percussion and a tympanitic note on superficial percussion.

11th. Examined by Professor Kehr. Diagnosis: Stone in the common and cystic ducts; empyema of gall-bladder and chronic interstitial pancreatitis.

14th. Had a hemorrhage last night, lost twenty ounces of blood. Patient was not conscious of the passage of blood. Slept very well all night.

16th. Slept very poorly last night. Has much pain on both sides near the edges of the ribs. The pain radiates to the back.

18th. Bowels moved five times yesterday. The first stools were well formed, but the last were quite soft. There was blood in all of the stools.

19th. Had a large hemorrhage from the bowel this afternoon; following which he became rapidly weaker and died.

Urine Examination. Specific gravity 1020; acid; bile present; albumin, sugar, casts, and indican absent.

Feces. Gallstones absent.

Blood. May 9th, red, 3,250,000; white, 9000; hemoglobin, 65 per cent. May 16th, red, 3,5000,000; white 10,000; hemoglobin, 65 per cent.

Autopsy. (By Dr. H. C. Carpenter.) Body of white man apparently about forty-five years old, intensely jaundiced, golden in color. Body emaciated; a scar about five inches in length is seen in right inguinal region, over Poupart's ligament. Abdomen is distended and tympanitic. On section all organs are likewise jaundiced.

Heart is negative, except for slight sclerosis of mitral leaflet, but no stenosis. Lungs negative. Spleen is normal in size. Kidneys moderately enlarged, swollen, and capsule strips easily. Liver: enlarged and tissue is somewhat friable. There is an extensive peritonitis in gall-bladder region; the gall-bladder and

surrounding organs are bound together by adhesions. The gall-bladder is very large, and part of its interior surface is gangrenous; contains about a pint of chocolate-colored, inspissated bile, but no stones. The pancreas is slightly harder than normal, and a large tumor is present in head of pancreas, which is pressing on the bile-ducts. The tumor is about the size of an orange; on opening it is seen to be an organized blood-clot, not recent in origin. The hemorrhage was originally into the pancreas and surrounding tissue, and became encapsulated. The intestines are distended; no ulcer discovered. Appendix normal, but unusually long. The clot in pancreas is laminated, and in one spot a recent hemorrhage is visible. The pancreatic duct was distended. No stone discovered. There was no fat-necrosis noted.

Discussion.

Dr. J. A. Scott said that hemorrhages of the pancreas are usually small and scattered throughout the entire substance. He had never seen hemorrhage of the type presented by Dr. Stahl's specimen in hemorrhagic pancreatitis. Even in the case of small hemorrhage, fat-necrosis is usually present. The symptoms in Dr. Stahl's case did not seem to Dr. Scott to be typical. The clinical picture usually resembles that of acute metallic poisoning. The speaker thought that the hemorrhage might have come from an aneurysm of the abdominal aorta.

Dr. Coplin said that he had made autopsies on two cases in man and on one in a dog. In the latter there was no evidence of biliary obstruction. In one of the human cases there were signs of retrojection of bile, the pancreatic duct having been bile stained to its middle. In all, there were widespread fat-necroses.

Dr. Hawke said that he had seen two cases in the Insane Department of the Philadelphia Hospital. In one, there was a sinus leading from the stomach to the pancreas; in the other, the hemorrhage was larger than in Dr. Stahl's case. The clot was partially organized and soft in the centre. Dr. Hawke said that he should like to know whether others had seen any cases of pancreatic hemorrhage in the insane.

Dr. Stengel asked Dr. Stahl the duration of the case.

DR. STAHL said that the total duration of the case was eleven weeks.

DR. STENGEL, continuing, said that some authors make a distinction between hemorrhage into the pancreas and hemorrhagic pancreatitis. The clinical picture of these two conditions is often identical. In hemorrhagic pancreatitis the hemorrhages are small and disseminated, and are accompanied with inflammation; in hemorrhage into the pancreas the hemorrhage predominates, though there is some reactive inflammation. A third condition to be kept in mind, said the speaker, is hemorrhage into the lesser peritoneal cavity. He had seen one of Dr. Hawke's cases in which he himself was wrong and Dr. Hawke was right.

DR. STAHL suggested that the Society take charge of the specimen; and on motion it was referred to the Committee on Morbid Growths. *February* 11, 1904.

Report of the Committee on Morbid Growths Concerning Dr. Stahl's Specimen.

The specimen consists of the lower portion of the duodenum, including the papilla, the body and tail of the pancreas, and a huge blood-clot the size of a fist. There is also a section of the inferior vena cava attached to the mass. The tail and body of the pancreas are of about normal width and thickness, but on section the tissue seems to be extensively infiltrated with fat. The duct, about one-sixteenth of an inch in diameter, can be followed uninterruptedly to the point at which the clot is attached to the pancreas. There it is lost for a short distance. When a probe is passed from the papillary end it meets a probe passed through the distal part of the duct in a cavity in the pancreas which is not a portion of the cavity containing the clot, but appears to be a dilated part of the duct itself. The head of the pancreas cannot be made out; but in its position in the concavity of the duodenum there is the large blood-clot previously mentioned. The latter, therefore, lies directly in the hollow of the duodenum, under the papilla and the proximal portion of the duct. In its lower part, where it is not in contact with the duodenum, the clot is surrounded with a

thick adventitious sac, which seems to have ruptured on the lateral aspect of the mass. For the most part the clot is old and laminated; but there is a little recent blood beneath the point of rupture.

The splenic artery was searched for; and, so far as traceable, was found not to be atheromatous. Owing to the condition of the specimen, the artery could not be followed far. It did not, however, appear to enter the mass of clot.

The committee are of the opinion that a hemorrhage into the head of the pancreas has occurred. Its source they have been unable to determine; but they incline to the view that it may have been traumatic. There is no sign of any hemorrhagic pancreatitis or fat-necrosis; there is, however, distinct fatty infiltration of the pancreas.

EDSALL,
RIESMAN,
STEELE.

A Case of Xanthoma.

JOSEPH MCFARLAND, M.D.

The patient whom I present for your examination this evening suffers from widespread xanthoma of the face, hands, body, and feet, the lesions being exceptionally large and numerous. He is eighteen years of age, white, American, greatly stunted in growth, and suffers from occasional attacks of jaundice. The clinical data of the case are to be separately published by Dr. John V. Shoemaker, of Philadelphia.

The material subjected to microscopic examination consisted of a tumor about the size of a soup bean, which the patient permitted us to excise from the anterior aspect of the left knee, the excision being accomplished after the skin had been frozen.

As the nature of the lesion was not recognized at the time of excision, the specimen was, unfortunately, hardened in formaldehyd and rapidly imbedded in paraffin and celloidin, thus making it impossible through subsequent procedures to study the fats contained in the cells.

The excised tumor formed a node the surface of which was small, irregular, and was spotted with yellow. Some of these spots were the size of a pinhead, some considerably larger; their disposition was quite irregular. Pressure on the growth caused the patient slight pain; it was fairly firm to the touch. Vertical sections were made through the node. The changes observed can best be described in the following order:

1. The Epidermis. Most of the changes observed in the epidermis were atrophic in nature. The horny layer of the skin seemed to have undergone no change whatever, but in many places the rete mucosum was thin, and at irregular intervals along the surface this thinning was particularly observable because of the disposition of the papillary layer of the cutis vera. In one single spot there seemed to be parenchymatous degeneration of the cells of the rete with the formation of a small vesicle. No changes deserving mention were observed in the epithelial cells themselves, and their relation to the cutis was in nowise disturbed.

2. The Cutis Vera. (*a*) *The Papillary Layer.* As has already been stated, the papillary layer of the skin was irregular in that at frequent intervals along the edge of the section the papillæ were entirely absent, the epiderma above these points being very much reduced in thickness and the cells small and atrophic. In general the papillary layer was not otherwise disturbed, but at occasional intervals an invasion of the tissue by the peculiar cells yet to be described could be observed.

(*b*) *The Reticular Layer.* The chief changes were to be found in the reticular layer of the cutis, and consisted of an invasion of its tissue by cells whose characteristics were very striking, but whose histogenesis was obscure. These cells, which have been described by many histologists as *xanthoma* cells, penetrated the tissue of the reticular layer irregularly in a manner resembling the invasion of the areolar tissue by carcinoma cells. There was, however, for the most part a denser aggregation of cells and a less limited extension from the older masses than is to be observed in carcinoma. The cells were large, at first glance suggesting those of the sebaceous glands. This resemblance corresponded in size, shape, transparency, proportion of cell substance, nucleus, and in the presence of large numbers of fat droplets in the cytoplasm. The

cells were sharply defined by what seemed to be distinct though thin cell walls. They were flattened by mutual contact. In the central portions of the large aggregations, where they were presumably oldest, they were largest and contained the greatest number of droplets. The nuclei of these cells appeared slightly shrunken. As one passed from the central to the peripheral portions of the cellular aggregations it was found that with rare exceptions they possessed no distinct limitation, but extended as a continuous reticulum throughout the fibroelastic framework of the cutis vera. The extending bands of cells presumably occupied any interspaces and possibly the lymphatics, though it could not be made out that they were in any way limited by the endothelial cells of the lymph spaces. The peripheral extensions consisted of smaller cells of cuboidal shape, with more distinctly vesicular nuclei, with greater affinity for the stain than those of the older central cells, and contained fewer and smaller fat droplets.

(*c*) *The Subcutaneous Tissue.* The cellular extension did not invade the subcutaneous tissue, the whole extension appearing to be confined to the reticular layer of the skin, with occasional extensions into its papillary layer.

In considering the appendages of the skin some striking peculiarities were observed.

1. *The Hair Follicles.* Of these there were very few, the hairs being very small. So far as could be observed there were no pathologic changes in the structure.

2. *The Sweat Glands.* The ducts of the sweat glands could not be followed in any of our sections from the surface to the glandular coil, but numerous of the sections passed through the ducts and the coils, and examination of many of these glands failed to show any departure from the normal. The xanthoma cells, however, seem to follow the sweat glands in their greatest extension, and in many places came into quite intimate relation with them, and not infrequently masses of the xanthoma cells were found to have aggregated about the sweat glands.

3. *The Sebaceous Glands.* One of the most striking features of the sections was the total absence of sebaceous glands. The skin of the knee probably possesses few of these appendages, but in

general the distribution of the sebaceous glands coincides more or less perfectly with that of the hair follicles, and one would expect to find sebaceous glands in connection with the hair follicles observed. This, however, was not the case. No structures that could be definitely made out as sebaceous glands were present. Though some of the characteristics of xanthoma cells at first glance present a close resemblance to them, it was found in all cases that these characteristics were without ducts and devoid of the sharp limitations characterizing these glands.

4. *The Bloodvessels.* Capillary bloodvessels were quite numerous throughout the tumor, in many cases being formed of more or less densely cuboidal cells and presenting an embryonic appearance, so that it seems justifiable to infer that new capillaries had been formed during the development of the growth.

The histogenesis of the xanthoma cells is the most perplexing feature of the tumors. The first theory that suggests itself is that the cells are derived from those of pre-existing sebaceous glands, and that the entire growth results from an irregular and atypical multiplication of sebaceous cells analogous to the carcinoma development of other glands. This, which is one of the oldest theories, has in its favor the resemblance between the xanthoma cells and the sebaceous gland cells, the presence of molecular fat in the cells, the lack of sebaceous glands in the tumor, and the known ability of glandular cells to lose their normal arrangement and take on a heterogeneous distribution when excited to neoplasmic development. But the theory is completely disproved by the frequent occurrence of the xanthoma masses in the mucous membranes and internal organs where there are no sebaceous glands.

Antagonistic to this view and completely disproving it, should the histology of the two lesions be identical, is that typical xanthoma nodules are said, upon excellent authority, to be found in the internal organs as well as in the skin. So that unless these could be regarded as metastatic growths the development of the tumor from sebaceous glands is inconceivable.

The second theory, which seems to have no foundation, is that the growth results from changes in muscle fibers, and that what seems to be epithelial cells are in reality nothing but altered muscular fibers. This view was advanced in consequence of the study

of a case of xanthelasma, a closely related and probably identical condition observed upon the eyelids, and as the skin in these structures is in intimate relationship with the fibers of the orbicularis palpebrarum muscle, and the characteristic cells may in some cases invade the superficial layer of muscular fibers, the opinions may have been justified. It is, however, scarcely conceivable that a growth limited to the skin of the knee, not invading the subcutaneous tissue, and embracing an area of skin containing extremely few hair follicles, and, therefore, whose only muscle fibers could be one or two tiny arrectores pili muscles, could have such an origin.

Finally, it is held that the cells are of endothelial origin, and are derived from the cells normally present in the lymph spaces and channels. Should this be the case the growth is to be regarded as a species of endothelioma, but it is entirely unlike other endothelioma, in that the cells attain to such large dimensions and that they accumulate molecular fat. The assumption of molecular fat is not known to be a peculiarity of endothelial cells. The formation of molecular fat is, however, a peculiarity of certain epithelial cells, as, for example, those of the milk and sebaceous glands.

It is very important to consider the source of the fat globules present in the cells. Either they must be formed in them or they must be conveyed to them. The general appearance of the growth whose cells are so uniformly, from the oldest down to the youngest, filled with molecular fatty matter might suggest that the fat is formed in them and by their activity, and the magnitude of the cellular characteristics and their reticular distribution make it almost inconceivable that there are any cells normal to the part which have become infiltrated with fat. All the appearances justify the belief that the cells belong to some genus whose members have a normal fat-forming or fat-storing tendency, and that these cells so endowed multiply and penetrate into the tissues and continue in all directions their normal tendencies.

Discussion.

Dr. Hartzell said that the case is a striking example of an extremely interesting disease. This variety of xanthoma is quite rare; but xanthoma palpebrarum, a closely related affection, is not uncommon. The pathogenesis of these cases, said the speaker, is undetermined. Though various theories have been advanced as to the origin of the cells infiltrating the skin and producing the new growth, there are objections to and inconsistencies in all of them; and some can be positively disproved. Many cases show jaundice, though this is by no means invariable. The patient exhibited showed jaundice and enlarged liver. The disease is chronic, and may last for months or years, and may disappear spontaneously. Histologically, the condition is fatty infiltration, and not a degeneration; so that its disappearance is always possible. The speaker had seen cases in which the jaundice was more marked, and in which the tumors in the skin were as large as hens' eggs, and bright yellow.

Dr. Eshner had noticed an obvious feature of the case that had escaped mention by the previous speakers—namely, a symmetric distribution of the lesions, especially affecting the flexures as seen in the palms, at the wrists, the elbows, and the folds of the axilla. At the periphery they have a distribution resembling carcinosis.

Dr. Stengel congratulated Dr. McFarland on his interesting presentation of the patient, with microscopic slides of the lesions. He felt that the close relation of pathology with practical medicine was thus made apparent. Dr. Stengel referred to specimens of xanthoma palpebrarum which had been taken from a physician who had permitted him to excise portions for pathologic study. This condition has been quite common in his experience, and he has found it characterized by a remarkable variability in the conspicuousness of the lesions. The latter appear and disappear without discernible cause, or in consequence of various derangements of health. He agreed with Dr. Eshner that the peculiar distribution of the lesions in Dr. McFarland's case suggested extension along some channels of circulation, most likely the lymphatics.

Dr. McFarland, in closing, said that Crocker, in his text-book, speaks of one case that recovered spontaneously. From studying

the sections, one gets the idea that the disease may be self-limited; because there seems to be a dissolution in the center of the cell-groups, while there is continued invasion of the periphery. If the balance is in favor of invasion, the disease continues to spread; if, however, it changes and favors destruction of the cells, it may recover. *December* 10, 1903.

Uremic Hemiplegia, with Changes in the Nerve Cells of the Brain and Cord, and Recent Primary Degeneration of the Central Motor Tract.

T. H. WEISENBURG, M.D.

(From the William Pepper Laboratory of Clinical Medicine, Phoebe A. Hearst Foundation, and the Philadelphia General Hospital.)

ABSTRACT.

Some of the effects of the condition known as uremia upon the central nervous system have been well recognized. Hemiplegia of uremic origin is not very rare, but its cause has always been in doubt. The findings at necropsy have usually been more or less edema of the brain substance and its membranes, and at times dilatation of the ventricles.

The cellular changes in the central nervous system in experimental uremia of lower animals have been carefully studied by numerous observers. The changes described consist chiefly in a chromatolysis of some of the cells of the anterior horns of the spinal cord, of the cerebral cortex, and of the cerebellum. These changes, however, are not characteristic.

Ewing studied microscopically the nerve cells of the brain and cord of six cases of uremia. In none of his cases was there any accompanying paralysis. The nerve cells, especially those of the medulla, were in an advanced stage of chromatolysis. The alterations in the cells of the anterior horns of the spinal cord and in the cortical cells were not very marked or uniform in character.

The first case here reported was a woman, seventy-one years of age, admitted to the nervous wards of the Philadelphia Hospital from the out-wards. She had a left-sided hemiplegia, which per-

sisted for fourteen days before she died. At the necropsy the kidneys were found in a state of chronic diffuse nephritis. Sections of the brain showed no gross lesions. There was no note made at that time of edema of the brain or membranes.

The second case was that of a woman, seventy-seven years of age, who had also a left-sided hemiplegia, which persisted for four days before death. At the necropsy, the kidneys were small and showed changes characteristic of chronic diffuse nephritis. Macroscopically there were no changes found in the brain or cord.

Microscopic Examination. First Case. The nerve cells studied were taken from the anterior horns of the spinal cord, cervical and lumbar regions, medulla oblongata, paracentral lobule, temporal, frontal, and occipital lobes of the cerebrum, and from the cerebellum. There was advanced chromatolysis, especially in the Betz cells of the paracentral lobule, which was more distinct in the side opposite the paralysis. The alterations in these cells were not uniform. The cells of the anterior horns of the spinal cord, medulla oblongata, and cerebellum were not much altered. A careful examination showed that there were no minute areas of softening, nor the lacunæ described by Marie, present in the brain.

A degeneration of the fibers of one motor tract as shown by the Marchi method, was traced from the lumbar region of the spinal cord to the internal capsule. The degeneration while not intense was unmistakable, and was of such character as would be expected in a primary degeneration of recent origin, in this case fourteen days. It was most marked in the left crossed pyramidal tract of the cervical region, and became less intense in the medulla oblongata and cerebral peduncle; in the internal capsule it was hard to find traces of it.

The degeneration was essentially a primary degeneration, and in association with the changes in the nerve cells in the motor cortex. That the degeneration was found only in the motor fibers of one side is explained by the more intense alterations in the cortical cells belonging to these fibers, and it is a fair presumption that had the uremic poison or poisons had time to act further, there would have been also a primary degeneration of the motor

fibers of the opposite side. The term primary degeneration is used here in the sense that it is not secondary to a gross lesion.

In the *second case*, changes were found in the nerve cells, but these were not as marked as in the first case. No degeneration was found in the motor tract, but this was hardly expected in a case of four days' duration.

As a result of the study of these cases we must come to the conclusion that a toxic process, as uremia, may produce definite changes in the nerve cells of the brain and spinal cord, and that these changes may be more marked in the motor cells of the cortex; and that in association with these alterations in the nerve cells of the motor cortex we may have a primary degeneration of the motor fibers, providing the duration of the hemiplegia is long enough.

December 17, 1903.

Proceedings

of the

Pathological Society of Philadelphia.

MARCH, 1904. NEW SERIES, VOL. VII., NO. 3.

TABLE OF CONTENTS.

COPLIN, Changes in the Intercostal Muscles and Diaphragm in Infective Processes Involving the Lung and Pleura.—LOEB, Some Recent Contributions to the Etiology of Cancer.—MULLER, A Case of Pancreatic Lithiasis with Atrophy and Lipomatosis of the Pancreas, Associated with Pulmonary Tuberculosis.—HOWARD, A Case of Filaria Immitis in the Heart of a Dog (presented by DR. RIESMAN).

Changes in the Intercostal Muscles and Diaphragm in Infective Processes Involving the Lung and Pleura.

W. M. L. COPLIN, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

So far as the writer is aware no important study has been undertaken of the relation, if any, existing between the intercostal muscles and inflammations of the lung and pleura or either alone. An examination of the most important text-books on medicine and pathology discloses no reference to characteristic anatomic changes in the intercostal muscles or nerves, in any of the conditions under consideration.

Aufrecht,[1] in a most exhaustive article on pneumonia, notes the occurrence of severe intercostal pain and pain in the abdominal muscles, both of which are attributed to the cough, and this seems to be the view held by other observers. It is reasonable to assume that the cough induces muscular soreness comparable to the soreness resulting from any other form of muscle fatigue, but, in some cases at least, muscle pain and tenderness may depend upon demonstrable lesions in the affected tissues.

Rosenbach,[2] in his elaborate article on pleurisy, speaks of atrophy of the thoracic muscles and antagonistic muscles, and briefly refers[3] to the fact that changes occur in the costal pleura and intercostal muscles during perforation.

Again,[4] without any special detail as to the character of the lesions, he refers to degeneration of the thoracic muscles in acute and chronic pleurisies. The same writer notes that certain of the sensations apparently arising in the intercostal spaces resemble muscle pain,[5] and that in large exudations where muscles and pleura are "much involved," the intercostal depressions are obliterated so as to admit of deep pressure. He does not refer to these phenomena as indicating a period of relaxation in the muscle, although that seems to be the probable explanation.

In an editorial note Musser refers to a case in which pleurisy and intercostal neuralgia were concurrent. In the first week pleurisy signs dominated; in the second, third, and fourth weeks intercostal neuralgia was most evident. An herpetic eruption developed along the course of the ninth intercostal nerve.

Rosenbach[6] refers to marked dyspnea, if there be much pain in the thoracic muscles, and speaks of rheumatic pains in these muscles as accompanying dry pleurisy. In common with other observers, he[7] notes the respiratory asynchronism evinced by delayed excursion on the affected side. The chest deformity associated with contracting thorax, he says, may be due to degenerated and contracted muscles,[8] and the intercostal spaces may be obliterated, the ribs overlying each other like tiles on a roof.

The same writer[9] is of the opinion that in affections of the thoracic muscles—such as rheumatism and intercostal neuralgia—contraction of the intercostal muscles may give rise to conditions that simulate dulness. At just this point it may be well to note that edema, perivascular infiltration, and lipomatous change of the intercostal muscles would, theoretically, favor the same result. With full recognition of his entire unfittedness, it is not the writer's purpose to discuss the influence of the alteration in the intercostal tissues on physical signs; but any of the mentioned changes in the intercostal muscles would presumably influence the percussion note and probably modify the auscultatory sounds.

With regard to the pseudopleural friction sound, called by the French "*bruit de cuir neuf*," Rosenbach[10] accepts the condition as a muscle phenomenon, and it is not improbable that other pseudopleural friction sounds are, at least in part, of muscle origin. As will be shown later, pleurisy may be complicated with a myositis.

and it would be of great interest to know if any friction sound results from movement in muscles the seat of inflammation. This could be determined, probably with great accuracy, by auscultation of muscles so situated as to exclude the probability of friction sounds arising from any other cause. It is well known that edema of collagenous membranes, such as tendon-sheaths, may give rise to friction sounds, and it is not impossible that the septal fibers or septal membrane between the external and internal intercostals, and possibly the movement of fiber sheaths or bundles one upon another, might give rise to such friction.

Przewalski[11] calls attention to the narrowing of the intercostal spaces and increased resistance to intercostal digital pressure in all of nineteen cases of pleurisy, fourteen of which were serous and five suppurative. The sign is most easily elicited in children. He regards this narrowing of the intercostal spaces and fixation of the intercostal muscles as characteristic of pleurisy and analogous to "les attitudes fixes des membres" in inflammations of the joints. He does not seem to have suggested that the phenomenon that he observed could have depended upon architectural change in the muscles of the area to which he draws special attention.

Although Rosenbach[12] speaks of extension by contiguity from pleura to peritoneum, the anatomic changes in the diaphragm accompanying such extension received no specific notice. The only study of the muscles of respiration in pneumonia and pleurisy with which I am familiar is that by Rohrer.[13] This observer made a careful study of the diaphragm in pneumonia, pleurisy, and pericarditis, and shows that in pneumonia and pleurisy an interstitial myositis of the muscular portion of the diaphragm adjacent to the area involved—whether it be pleura, pericardium, or peritoneum—frequently results. His studies include only lesions of the muscle areas of the diaphragm; he makes no reference to any involvement of the tendon. His excellent paper is illustrated by a number of exceptionally good photomicrographs of the condition that he describes. This phrenitis or diaphragmitis, Rohrer believes, may result from (1) direct extension, (2) extension by the lymphatics, and (3), though rarely, hematogenous infection.

Personal Observations. The writer has studied the intercostal muscles in seven cases; two of these were croupous pneumonia with plastic pleurisies, the pneumococcus being isolated from the lung and pleural effusion. Two were tuberculous lesions of the pleura; one of them a direct extension of tuberculosis to the pleura from a large area of recent tuberculous pneumonia, in the presence of a dense fibrous adhesion, irregular in outline, 12 cm. in length anteroposteriorly, and possessing a maximum breadth of 6 cm., situated immediately over and involving the lower portion of the upper lobe of the right lung; the anterior margin of the sclerotic area corresponding to the costocartilaginous junction. The other case was a frank tuberculous serofibrinous pleurisy, acute in time, the tubercle bacillus being demonstrable in films from the exudate, and the condition associated with a number of chronic tuberculous lesions of the lung, some of which were fibroid, partly encapsulated, others evidently more recent. Two other cases were acute pneumococcal pleurisies: one in a child seven years of age, the other in an adult and associated with pericarditis. The seventh case was a chronic empyema for which Professor Keen performed an extensive resection of the thoracic wall.

In both cases of croupous pneumonia the diaphragm was also examined. One case showed the acute leukocytic infiltration similar to that described by Rohrer with, at points, evident beginning abscess formation. This is evinced by areas of necrosis extending the breadth of six to eight muscle fibers, the necrotic detritus being richly infiltrated with polymorphonuclear and hyaline leukocytes. At such points, by appropriate staining methods, organisms possessing the morphology and tinctorial characters of the pneumococcus can readily be demonstrated. The change not mentioned by Rohrer, but clearly made out in this case, is an evident involvement of the lymphatic tracts of the tendon of the diaphragm. Sections of this tissue show irregular columns of leukocytes arranged parallel with the fibers, and sometimes so solidly grouped as to constitute, almost, an injection of what appears to be a lymph vessel. Within the muscle area and occasionally in the tendon the fibrin-content of the exudate can be demonstrated satisfactorily by Weigert's fibrin stain.

Fragmentation of the muscle fibers and the appearance within them of phagocytic leukocytes would indicate that an attempt was being made to clear up the areas of necrosis by the ordinary process for the removal of necrotic tissue. In this particular instance I have found no evidence of further effort at repair. The acuteness of the process probably explains this finding. The change in the muscle so far as can be determined from the examination of a single specimen, is restricted to the side involved. In the tendon, however, the lesion is a little more diffuse. The diaphragm in the other case of pneumonia and also the intercostal muscles in the same case show practically no structural alteration, at least nothing that could not be attributed to such variation in spacing of fibers and in size as might be found in any muscle.

The changes found in the other five cases may be grouped together with the case of acute tuberculous pleurisy. They were not marked. In the other case the lesion is much more advanced and, later, will be described in detail. In the two acute pneumococcal infections engrafted on catarrhal pneumonia, the lesions are evident and clearly recent; the one chronic case must be considered separately.

The number of cases examined is, of course, too small to determine with accuracy, and, to the satisfaction of the critical observer, the exact order in which the lesions occur. Probably the following order will require revision upon more extended observation; it is at present submitted more for the purpose of indicating the character of the lesions found than with the idea of definitely establishing the chronologic order in which the processes occur.

1. Muscle fibers showing marked granular change, inadequate tingibility, and unsatisfactory stain reaction, such as commonly observed in glandular tissues, can be recognized in all cases. It is not clear that this granular degeneration or cloudy swelling can be attributed to inflammation in the adjacent serosa, as it closely resembles, indeed is probably identical with, the cloudy swelling observed in muscles as a result of infectious processes where apparently the toxin is acting through the blood. It would, therefore, seem wise to regard this change as part of an alteration affecting the general musculature, the intercostals, in common

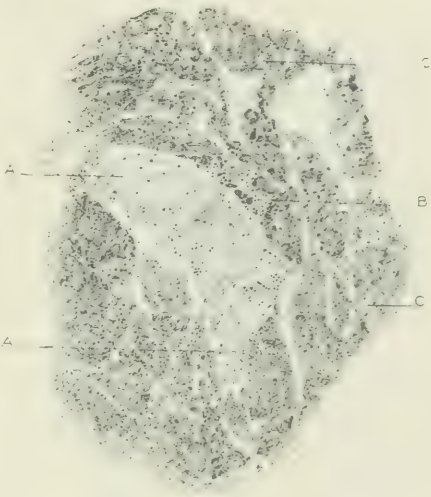
with other muscles, manifesting their share in the change induced by the systemic action of toxic bodies.

2. With this alteration probably begin the changes that are incident to the involvement of and extension from the adjacent serosa. Muscle fibers are dissociated, the separation in some instances being quite distinct. The presence of a granular acidophilic deposit around the muscles and interfascicular connective tissue indicates that we are dealing with an edema; but few leukocytes can be seen in this stage. The muscle cells stain poorly, the connective tissue does not respond with its wonted activity to the usual connective-tissue dyes. The component cells are swollen and granular, and occasionally a faint network of fibrin can be demonstrated at selected points. There is not, however, in this stage, any conspicuous addition of any fibrin-containing substance. With this condition bands, groups, and bundles of muscle fibers may be seen showing a change that, so far as I can observe, cannot be differentiated from the hyaline, vitreous, or diaphanous degeneration described by Zenker, known to occur in the muscles of the abdominal wall in typhoid, and now recognized to be a much more widely distributed lesion often found in other conditions. In these hyaline areas muscle fibers often appear to coalesce so that the hyaline change seems to include the interfascicular tissue as well as the muscle fiber. Whether this change be a secondary degeneration or necrosis, probably our present methods are inadequate to determine. That it is not identical with coagulation necrosis containing fibrin can easily be established by the absence of fibrin in some areas where the process now under consideration is conspicuous; we are familiar with processes clearly necrotic and closely resembling, if not identical with, the change now under consideration, that could not, with propriety, be grouped with the necroses. As this, however, is neither the time nor the place to enter into the academic discussion as to what constitutes necrosis and what degeneration, it does not seem necessary to consider further the change present, the appearance of which is fairly well reproduced in Fig. 1.

3. It seems reasonable to assume that the stage now to be described is preceded, at least in some instances, by the alterations mentioned above. The dissociation of the fibers, the gran-

ular material, the areas of hyaline change, can still be recognized or at least appearances of their having been present may be more or less fully identified. In this stage there is a leukocytic infiltration of the muscle similar to that shown in the photographs illustrating Rohrer's article. The leukocytes present in the specimen studied are mostly of the mononuclear type, many of them corresponding to the large lymphocyte or hyaline cell; the polymorphonuclears have not been exceedingly numerous; eosinophiles have not been identified in the altered area. The dissociation,

FIG. 1.



Intercostal muscle, transverse section, from a case of epipneumonic pleurisy, showing area of necrosis. Tissue fixed in Zenker's fluid; hematoxylin and eosin stain. A, A. Necrotic area in some portions of which the shadowy outlines of muscle fibers may still be distinguished. B. A few mononuclear leukocytes, mostly of the lymphoid type, aggregated on the margin of the necrotic area. C, C. Fragmenting vacuolated fibers, of which several can be seen in the field.

fragmentation, granularity, and necrosis of the muscle fibers are, in this stage, very much more evident. It is a diffuse process; some of the fibers appear to suffer to a marked degree, almost amounting to a necrosis, while others but slightly altered may be seen immediately adjacent, in a way resembling very closely the myocardial degenerations that have been described in various infectious diseases. (See Fig. 2.) Fibrin is abundantly present; bacteria may be conspicuous, while in the preceding forms they were at most but scanty and usually absent. There is, in this stage, no difficulty in the identification of organisms that, in the pneumonias and epipneumonic pleurisies, may, with reasonable

certainty, be considered pneumococci. Sometimes the bacteria are grouped in the spaces between the muscle fibers in such a manner as to indicate dissemination along a lymph vessel, possibly only a larger lymph space.

It has not been possible to secure specimens showing what might be looked upon as the next stage, and as to the ultimate outcome, should the patient recover, it is not possible at the present time to offer any unassailable opinion. Evidence of abscess formation is usually absent; the process seems more diffuse, but one could easily appreciate that the small necrotic areas infiltrated

FIG. 2.

Intercostal muscle, transverse section, from a case of epipneumonic pleurisy, showing dissociation of fibers, interfascicular leukocytic infiltration, and slight fibrin formation. Tissue fixed in Zenker's fluid; hematoxylin and eosin stain. A, A, A. Granular and fragmented muscle fibers. B. Accumulation of leukocytes and fibrin around and extending between the muscle fibers. In some areas the change is more marked than in others, and at points many polymorphonuclear leukocytes can be seen.

by polymorphonuclear leukocytes are really microscopic abscesses, such as can readily be demonstrated in the diaphragm. Our knowledge of the pathology of muscle inflammations would lead us to infer that with the subsidence of active infection the necrotic muscle fibers would be removed by phagocytic cells (myoclasts); the interfascicular exudate would undergo absorption and, with the formation of a certain amount of fibrous tissue, there would eventually result a moderate degree of muscle sclerosis. It therefore seems reasonable to assume that where the disease lasts a

sufficient length of time—where, in other words, the infection is permitted to continue—the changes between the stages just described and the conditions found in the specimen examined and reported below would fall under the head of subacute or chronic sclerosing myositis, which, toward the end, would give rise to the picture presented in the following case.

For the privilege of reporting this case I am under particular obligations to Professor Keen, who kindly placed at my disposal his notes and description of the operation from which I summarize as follows:*

F. A., male, aged twenty-two years. Admitted to the Jefferson Hospital on June 11, 1903. Patient of Dr. Boyer.

Left-sided pleurisy for six years' duration, terminating in empyema. Upon admission to the hospital the left side of the chest was fuller than the right. The intercostal spaces obliterated. Mediastinal organs displaced to the right. June 9, 1903, aspiration: three quarts of yellowish pus withdrawn. On June 16th Dr. Stewart excised two inches of the seventh rib on the left side at the anterior axillary line, opened the pleural cavity, evacuated a large quantity of greenish-yellow, turbid fluid, and inserted two drains. Bacteriologic examination by Dr. Rosenberger at this time showed cultures of the Micrococcus pyogenes aureus and albus. The urine contained albumin, hyaline and granular casts. Under drainage the patient improved and left the hospital on June 28th. Daily irrigation of the cavity was practised for some time before leaving the hospital. He was readmitted under Professor Keen's care on October 26th. The heart was still displaced somewhat to the right; the left side of the chest was still flat; diminished resonance over left lung, with respiratory sounds diminished in upper and absence in lower half of organ. Urine contains trace of albumin, but casts were not detected. Tubercle bacilli were not found in the discharge from the pleura. Pneumococci noted as absent. Staphylococcus pyogenes aureus still present, and an organism possessing the morphology and tinctorial characters of the diphtheria bacillus, but without pathogenic action for animals, was obtained in studies made by Dr. Rosenberger.

* The physical signs were characteristic and need not be detailed.

*

On November 4th Professor Keen again submitted the patient to operation, and the following record is from his notes:

"I made the usual large flap extending from the second rib, with a broad sweep under the arm down to the level of the seventh rib, and backward between the scapula and the spine. The entire thickness of the chest-wall, including a greatly thickened pleura, was then removed from the third to the seventh ribs inclusive. The pericardium and pleura were exposed. I made no attempt at decortication, but only curetted the parts thoroughly, because the patient's condition was bad, with his heart pushing over to the right side, the left lung of very little use, and the right hampered by the displacement of the heart and the left lung; the operation was finished as rapidly as possible; after replacing the flap, which left a large opening at the lower portion, and packing some iodoform gauze to check the slight oozing, the wound was closed.

"On December 2d there were evidences of a beginning edema of the lungs: he rapidly failed and died on December 4th."

No autopsy was obtained.

The specimen removed came to the laboratory for study, and was submitted for examination to Dr. Ellis, Demonstrator of Morbid Histology, whose report is as follows:

"The specimen consists of a number of pieces of ribs, varying from 2 to 9 cm. in length, to which are attached masses of tissue. Portions of this tissue are grayish in color, dense, and apparently fibrous. The surface of some of the masses is yellowish or yellowish-gray, and shows areas of necrosis. Small fragments of muscle are also attached.

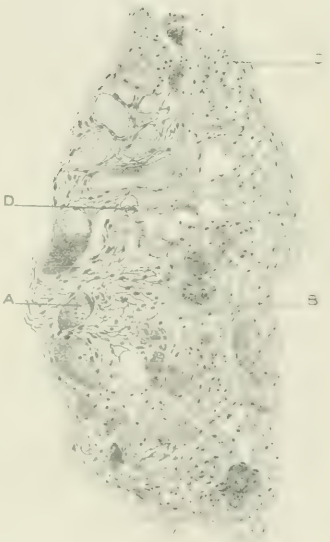
"The soft parts were fixed in Bensley's fluid, dehydrated, cleared, and infiltrated with paraffin. Sections were cut and stained by the usual laboratory methods.

"Microscopic examination shows the majority of the sections to be made up of fibrous tissue, most of which is in the early stages, though certain parts are quite dense. The margin of the sections bordering the most recent fibrous tissue is composed of embryonic and granulation tissues, in which are numerous polymorphonuclear leukocytes. Beneath this formative zone is fibrous tissue in various stages of formation. Some of the sections con-

tain considerable striated muscle which has undergone pronounced changes. Certain areas show a high degree of fatty infiltration, while in others this is associated with a marked increase of the fibrous tissue. The latter change is for the most part fairly recent in point of time. The muscle fibers show varying degrees of atrophy. Vacuolization and fragmentation of the fibers are also seen."

It will be observed that this specimen shows marked atrophy and advanced destruction of the muscle fibers, with intercalation of newly formed and forming fibrous tissue with, at points,

FIG. 3.



Intercostal muscle, transverse section, from a case of suppurative pleurisy of several months' duration, showing advanced fibrosis and lipomatous change. Tissue fixed in Zenker's fluid; hematoxylin and eosin stain. A. One of several granular fibers, some of which are fragmented and undergoing absorption. B. A small group of greatly shrunken muscle fibers. C. Relatively large mononuclear cell, not very abundant but commonly associated with fibroblastic elements. D. The leader from this letter passes between two imperfectly preserved fat bodies, a number of which are present in the newly forming or formed fibrous tissue. The fat content is scanty in the particular field from which this drawing is made.

advanced substitutive lipomatous infiltration. It seems reasonable to assume that the long-continued infection of the pleura has given rise to this alteration in the intercostal muscles. These structures, in this specimen, show no evidence of an existing infection. The process has assumed a very much more chronic type manifested by the development of formative tissue in the intramuscular septa and in the interfascicular spaces. Necrotic processes are no longer active in the muscles. Fig. 3 represents a small area from this

specimen, and shows to advantage the essential changes in the muscular tissue.

Pathogenesis. It seems to the writer that the cause of these changes in the intercostal muscles is clear. Feiner has shown that after injecting fluids containing suspended granules into the pleura the extraneous matter may be demonstrated in the costal pleural lymphatics, and that but little resorption takes place through the pulmonary pleura. When we consider the fact that in inflammations of the lung and pleura the inter- and intralobular lymphatic systems can be seen engorged with products of absorption from the lung principally, we can understand how the parietal or costal lymphatic,system must necessarily care for the major part of the drainage from the pleural cavity. This being the case, toxic materials passing off by this route are brought in close proximity to the intercostal muscles and diaphragm; it seems reasonable to assume that direct lymphatic paths may become occluded, being in close proximity to the centers of irritation, and, therefore, collateral currents must form through the intercostal muscles, thereby exposing them to the dangers induced by more or less persistent bathing in toxic lymph. If the infection be active or the resistance low, or both, the pathogenic organisms may be carried into the muscle, giving rise to suppurative processes, such as have been described by Rohrer, in the diaphragm, and figured in one of the preceding cases as occurring in the intercostal muscles. If the bacteria be scanty or of indifferent activity, or the patient's resistance high, they remain in the lung or pleura and the muscles, escaping direct infection, suffer from the toxic action only.

Where the irritation extends over a considerable length of time and granulation tissue with its protective influence against infection clothes the costal pleura, or where newly formed collagenous tissue is intercalated between the muscle and the altered serosa, then products reaching the muscle would probably be less active or materially modified toxins without evident bacteria. Here, then, results the chronic sclerosing change comparable to that seen in the muscles adjacent to tuberculous areas elsewhere in the body, as, for example, around tuberculosis of the hip, vertebræ, etc. In the acuter stages of the process the degenerative and necrotic

change seen in the muscles may be attributed to the action of the toxins passing through the lymphatics of the muscles or diffusing into the muscle tissue. In the later acute cases bacteria themselves enter. In the cases of longer duration there might occur a chronic suppurative interstitial and parenchymatous myositis, but probably the patient would not survive an infection of this type except purely as a local manifestation. The chronic alteration of importance is the sclerosing process by which the muscle is in part or almost wholly replaced by newly formed fibrous tissue in which fatty infiltration or lipomatous substitution almost constantly occurs.

The influence of the changes already described on the thoracic wall so fully suggest themselves that a detailed consideration need hardly be given. The clinician will at once think of the modifications in physical signs—muffling and alteration in auscultatory sounds depending upon increased density of the thoracic wall—brought about by any of the changes described, including serous infiltration, cellular accumulation, as well as fibrous and lipomatous change in the intercostal muscles; the influence of the change upon the function of these muscles will also be apparent. Even slight myositis is associated with rigidity—a more or less successful attempt at fixation—and this fully accords with the recognized clinical data.

A large amount of space might profitably be devoted to consideration of the influence of the change upon respiration, but as this is evident I need but touch upon the point. Hamberger's observations on the functions of the intercostal muscles in respiration has received general acceptance, and has been corroborated by the studies of Newell Martin and Hartwell, Masoin, and R. du Bois-Reymond.[11] The fact that the internal muscles are actively operative in respiration only when the function is labored renders more important the alterations now under consideration, because with alterations in the diaphragm—the principal muscle of respiration—and with the influence of intoxication upon the respiratory centers, and satisfactory evidence of narrowing of the intercostal spaces, as suggested by Przewalski, it becomes at once clear that structural alterations in these muscles must materially influence the alterations in chest volume upon which air intake so largely

depends. The fact that the external intercostal muscles are but slightly involved and often escape does not modify this observation, because physiologists are fully familiar with the fact that opposing muscles are reciprocally influenced. Mention should be made of the influence of sclerosing myositis in the production of costal fixation in the chronic cases: whatever views may be entertained with regard to the inexpansibility of lungs, long atelectatic, the condition of the ribs as regards motility cannot be ignored. The fixation of the affected side in acute cases may be, as is usually held, reflex, but it may also depend upon the spastic fixation of muscles (intercostal and diaphragmatic) the seat of pronounced architectural change.

Structural alterations in the intercostal muscles possibly clear up to some extent the observations that intercostal rheumatism, intercostal neuralgia, etc., are complicating or associated phenomena of pneumonia and pleurisy. In this connection there are several factors in this field that the writer appreciates are not worked out. Probably the most conspicuous is alteration of the nerves. Some of the sections show nerves that appear edematous. In none of them has any cellular infiltration been observed. The tissues have not been prepared suitably for the demonstration of myelin degeneration, and this question must be taken up with some detail later. I might at this point, however, say that sections show what histologists, so far as I know, do not mention, namely, that nerve filaments or even relatively large trunks can be seen coursing between the internal intercostal muscles and the adjacent pleura. They are so situated as to expose them to all the toxic substances permeating the adjacent muscle. In one block of tissue from an acute case two relatively large nerve bundles can be seen immediately below the serosa embedded in a small cushion of fat; the epineurium touches the serosa and a vessel lying in immediate proximity contains, on transverse section, seventeen erythrocytes, two polymorphonuclear leukocytes, and one hyaline cell; presumably a local leukocytosis. The nerve bundle is retracted from its sheath, on the inner aspect of which can be recognized transverse sections of two capillaries containing red cells, but no leukocytes; there is leukocytic infiltration of the sheath or nerve. Another specimen contains a longitudinal section of a

nerve that at one point shows a suggestion of cellular infiltration and contains a widely dilated capillary. Such axis-cylinder stains as have been applicable to Zenker material demonstrate no noteworthy change in the myelin sheaths and axis-cylinders of the nerves, but, as usual in such material, myelin stains have proven unsatisfactory. The foregoing offers no sufficient anatomic basis for the conclusion that the nerves suffer, nevertheless I am satisfied that in such instances as the one narrated they cannot long escape. Their perilous situation exposes them to the noxious influences of infection, toxic bodies and other coincidents of inflammation, to the action of which nerve elements are conspicuously susceptible. It would be interesting to know if the clinicians have observed any paralytic phenomena that indicate a toxic degeneration or neuritis involving the phrenic nerve or motor branches to the intercostal muscles. Alteration in the sensory fibers is strongly indicated by certain of the clinical factors; will the clinicians kindly advise us what, if any, symptoms or physical signs, point to motor involvement? I feel reasonably certain that there is no sufficient reason why the motor nerves should escape.

An extremely important point to be determined is whether there are any lymphatic ways corresponding to intercostal spaces in which this change is most marked. While I have no information that would justify a positive conclusion upon this point, the fact that well-marked changes may be seen in one area of an intercostal muscle, and the block of tissue from an adjacent neighborhood fails to show the alteration, leads to the belief that the lymphatic course or tract should merit special consideration, and it appears that in a very general way only have the anatomists and histologists solved this problem. Possibly we have in what might be called pathologic injection of the lymphatic spaces and vessels an important adjuvant in the study of the lymph courses. I have had no opportunity to study the changes in the lymph trunks draining the costal pleura; such a study, based upon experimentally produced inflammations of the lung and pleura, is needed.

An important question suggested by Dr. Riesman is, What would the intercostal muscles of the sound side show? In one of the cases of pneumococcal pleurisy the muscles of the other side escaped, or at least showed no structural change. I am not inclined to

believe that the opposite side is involved, unless thrombosis of the costal lymphatics of one side might lead to an anastomotic current passing to the other; such spanning of the mediastinum would seem improbable.

Another point upon which these studies are inadequate is the frequency with which the intercostal involvement occurs. Five of the seven cases studied are Philadelphia Hospital patients, and those familiar with the Blockley morgue know that we may draw incorrect conclusions as to the frequency of concurrent conditions because we are dealing with a class in whom coincidence of pathologic processes is a conspicuous feature.

Kuettner[15] has made an exhaustive study of the perforating lymphatics of the diaphragm. He shows that the drainage territories of the diaphragm are such that abundant opportunity is afforded for transdiaphragmatic infection, and has so worked out the lymph paths as to show that while each half of the organ possesses its own lymphatic field communicating with other parts by way of lymph nodes only, all parts of the diaphragm possess anastomotic communication with the pleura and peritoneum. The anterior and posterior lymph vessels communicate and drain in common into certain glands; some of these vessels vertically traverse the diaphragm twice in coursing over it. Taken with the studies of Rohrer and my own observations, it seems that Kuettner's work forms the necessary link in completing our already fairly full comprehension of the possibilities of transdiaphragmatic infections. That a juxtaposed abdominal viscus may infect pleura or pericardium (*e.g.*, hepatic, splenic, and perirenal abscesses and gastric ulcer) has long been common property, but that lesions of a finer texture may be recognized, and that the four great serous cavities are really intercommunicating lymph spaces, are within recent times leading to deductions some of which may be important. Is it possible that the pneumococcal inflammations of the peritoneum (even when primary) may be transdiaphragmatic infections, the lung and pleura escaping in some cases? The frequency with which the ribs suffer typhoidal osteomyelitis is suggestive, and if, as Fraenkel holds, the typhoidal spondylitis is really a bacillary infection of the cancellous tissues of the bodies of the vertebræ, the demonstration of abdominal and thoracic

lymph systems as so closely allied threatens, as the result of a minor disclosure, to lead one into a labyrinth of unjustified speculation.

It is not the purpose of this paper to consider transdiaphragmatic infections, the passage of fat-necrosing substances through the diaphragm, and cancerous extension from peritoneum to pleura, or the reverse; these subjects have recently been studied by von Brunn[16] and Jensen,[17] in pneumococcal peritonitis; by Henle,[18] in an article on "Pneumonia and Laparotomy;" by Truhart,[19] in considering intrathoracic fat-necrosis in disease of the pancreas, and by Tilger,[20] in pleurisy and peritonitis; Kuettner[21] discusses and gives most of the references. The demonstration of lesions in the tendon of the diaphragm is only a minor extension of Rohrer's observation.

In conclusion I wish to express my appreciation of the kindness of Professor Keen, and Drs. Rosenberger, Ellis, and Funke, for helpful aid in the preparation of material upon which this paper is based.

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Discussion.

Dr. Sailer complimented Dr. Coplin upon his valuable research. The nature of the degeneration Dr. Sailer considered interesting, and he thought that it might be toxic in origin. He had examined a case of bichlorid poisoning and had found extensive degeneration of the muscles, characterized by swelling of the fibers with loss of striation. Hyaline changes in the muscles, he said, were also present in typhoid fever.

Dr. Loeb asked whether Dr. Coplin had noticed multiplication of the muscle nuclei.

Dr. Coplin, replying, said that he had found no multiplication of the nuclei, but that he believed he might not have caught the right stage. He had meant to make clear in the body of his paper that absorption of the toxin probably occurred through the costal lymphatics with or without accompanying local dissemination of the bacteria. He intended to examine other muscles.

January 28, 1904.

Some Recent Contributions to the Etiology of Cancer.[1]

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(From the Pathological Laboratory, University of Pennsylvania.)

In giving the following brief review on some recent contributions to the etiology of tumors, I shall not be able to do more than indicate certain directions in which investigations are progressing, and to touch on some of the results obtained.

Anatomic researches of Wilms and others have shown that the so-called dermoid tumors frequently contain other structures besides skin and its appendages. Bonnet gave a uniform explanation of the origin of all these embryomata from misplaced blastomeres, or polar bodies, as Marchand had previously suggested. This hypothesis seems to have been readily accepted—almost too readily, it appears to me. Although it is not unlikely that it applies to many cases, it does not satisfactorily explain the fact that the majority of these embryomata are found in the reproductive organs. Bonnet's statement that a parthenogenetic development is impossible in vertebrates is not, as seems to have been assumed, a proven fact, but merely an hypothesis, which does not take into consideration that the first stages of a parthenogenetic development may be found in the mammalian ovary. Wilms, the last part of whose valuable work on mixed tumors was recently published, accepted Bonnet's views, and explains mixed tumors other than embryomata by anatomic or functional detachment of embryonic cells. Many of his conclusions will probably be modified by further research. A closer analysis shows that certain mixed tumors, as those of the thyroid, are probably not based on faulty embry-

[1] Read by invitation.

onic development. Experimentally, mixed tumors could never be produced by displacement of embryonal or adult tissues. Isolated blastomeres developed directly into a whole or a partial embryo without forming masses of undifferentiated embryonal cells, which Wilms finds in mixed tumors, and which seem to be necessary for explaining certain metastases. He finds transitions between mixed and single tumors, and claims for sarcoma the same origin as for mixed tumors. Carcinoma, he concedes, has a different origin. This distinction is, as can be readily seen, an arbitrary one.

Beard, who explains all tumors as originating from aberrant primordial germ cells, does not exempt carcinoma. His hypothesis does not at present need any further discussion, as the general occurrence of such aberrant germ cells has not yet been proven to the satisfaction of zoologists.

Of great interest is the fact, found in a number of cases, that tumors closely resembling chorio-epitheliomata may originate outside of the uterus. This, however, seems to be a very rare occurrence as compared with both the frequency of the detachment of chorionic epithelial elements and their transportation into the maternal body, and can, therefore, not be regarded as an argument in favor of the origin of malignant tumors from detached cells. In injecting placental tissues into pregnant and non pregnant animals L. Fraenkel obtained entirely negative results in regard to the production of tumors. Interesting is the fact that in teratomata of the testicle and ovary structures resembling chorio-epitheliomata have been found by Schlagenhaufer, Carey, Pick, and others. It has, however, to be taken into account that in otherwise normal mammalian ovaries structures may be found which, when assuming a rapid growth, will closely reproduce chorio-epitheliomatous formations. The fact recently found by L. Fraenkel, that lutein tissue is necessary for the normal course of pregnancy, is very suggestive, if we place it side by side with the findings of Poten and Vassmer, Stöckel, Runge, and others, according to which, in cases of hydatid mole or chorio epithelioma, a great overproduction of lutein tissue is found in the ovary. Similar tumor-like lutein formations can, however, exist without hydatid moles or chorio-epithelioma, as in a case observed in a

young calf. It seems almost as if we had in these cases a chemical explanation for certain tumors in the uterus in an excess of certain substances produced in the lutein tissue. However, at present this can only be regarded as a suggestion. Of interest also in this connection are certain tumor-like structures to be found in a certain percentage of otherwise normal ovaries of guinea-pigs, which structures later undergo retrogressive changes.[1]

The facts known in regard to the life and growth of tissues are as yet very insignificant. The experimental methods in this direction have, to a great extent, yet to be developed. It has, however, been found that epithelium can grow, without being in contact with connective tissue; that it can grow inside the body in such a substance as coagulated blood serum, and that epithelial cells may take up into their cell-body pieces of blood serum. Certain differences have been shown to exist in the growth of epithelium under such conditions and in the course of ordinary wound-healing. That an active growth of the epithelium, and not the activity of the connective tissue, is the primary factor in carcinoma, has been shown by Peterson, with the aid of Born's Reconstruction Method.

Great attention is still given to the attempts to prove the presence of a parasite in tumors by staining methods. There is one structure which has been much discussed in recent years, described by a number of older investigators, and later especially studied by Plimmer. This so-called Plimmer body appears as a round or oval vacuole, lined with a membrane, and including a small central round body, around which there is an unstained area. This body was interpreted by Plimmer as a blastomyces, and afterwards by v. Leyden as a protozoon. V. Leyden also drew attention to the similarity of these bodies to Plasmodiophora brassicæ, a myxameba causing the cabbage rot. Nawaschin and Behla had previously called the attention of pathologists, and especially of those investigating the cause of tumors, to Plasmodiophora brassicæ. The work of Plimmer and others was repeated by Gaylord, who, in his first publication, interpreted the Plimmer and Russel fuchsin bodies as a protozoon, and later as

[1] A fuller description of these structures will soon be published.

an organism similar to plasmodiophora brassicæ, as a myxameba. He injected plasmodiophora spores into rabbits, and found organisms resembling Plimmer bodies in phagocytic cells of the rabbit. He believes, therefore, that Plimmer bodies in tumors are also produced by mycetozoa.

In control experiments Aschoff and his pupil, Spirlas, found that injection of any animal cell or other material will produce the same appearances as Plimmer bodies in phagocytes. The experimental Plimmer bodies are nothing but vacuoles caused by digestion of included leukocytes. That Plimmer bodies are cell-vacuoles had already been maintained by Noesske, Greenough, Apolant, and others. The fact that Feinberg found that the central body stains with eosin in using the Romanowsky stain, just as the karyosoma of protozoa do, in contradistinction to the nucleolus of metazoic cells, which stain blue, is no proof of the protozoon character of this structure, because there exists variations in staining reactions of cell material. Feinberg interprets the Plimmer body as corresponding to an entire protozoon; other investigators regard it rather as corresponding to the nucleus of an organism. The distribution of Plimmer bodies, the fact that they occur almost exclusively in gland tumors, the fact that they cannot be seen in dividing cells, and the facts cited above, make it improbable that they are anything else but vacuoles. Recently Behla claimed to have produced Plimmer bodies and similar appearances by inoculating animals with certain unicellular organisms of vegetable character, the Chytidriaceæ. His conclusions as to the etiologic significance of these organisms are not well founded.

In recent years various intracellular enzymes have been found in different animal tissues. It is, therefore, not surprising that, following this line of thought, studies have also been made on tumors, to ascertain, if possible, qualitative or quantitative differences in the enzymes present in normal tissues and in tumors. Such investigations were carried on especially by Petry and Buxton. If we consider that our methods for the detection of ferments do not imitate the conditions under which the enzymes act in the living body, and if we also consider our as yet very rudimentary knowledge of the enzymes in normal tissues, it is not

surprising that the studies on enzymes in tumors have not thus far shown any significant difference between tumors and certain normal tissues.

Some valuable facts have been established by the statistic method. It is very probable that there is an actual increase in the number of deaths from malignant tumors, although the rate of this increase, it seems to me, has yet to be settled. It cannot be doubted that cancer may be endemic in certain villages, and even houses. Of especial interest is the fact that a similar endemic occurrence of malignant tumors has been found in animals. It has been observed in the case of carcinoma of the eye in cattle; it has been found by Borrel in carcinoma originating from glands of the skin in white mice, and it was found in the case of the cystic sarcoma of the thyroid in the white rat. In animals we can exclude many complicating factors which might come into play in man. Borrel, who is very skeptic in regard to the pretended parasites described by so many investigators, regards this endemic occurrence in animals as a strong argument in favor of a living organism as the cause of these tumors. Of great significance is the fact that in these cases the tumors were always of the same character in animals having lived in the same cage or on the same ranch.

In other directions, too, the study of cancer in animals is a promising field, offering the possibility of exact experimental investigation. Only recently have animal tumors been used for methodic researches into the etiology and structure of tumors, after it had been shown by older investigators that a number of tumors can be transplanted. It was found that the Berkefeld filter does not permit the causative agent of cancer to pass. Borrel had previously found that sheep-pox, a disease in which also a proliferation of epithelial cells may take place, is caused by an organism passing the Berkefeld filter. In a similar way it was found by Marx and Sticker that epithelioma contagiosum of fowl is caused by an organism passing a Berkefeld filter. It has recently been claimed by Hemmeter that he produced in a dog an adenoma by injection of a sterile filtrate of a tumor from another dog; but I think it may with great probability be assumed that the injection of this sterile filtrate did not produce a real tumor. It should be considered that around the edge of an experimental gastric ulcer

in animals a considerable inflammatory thickening may be produced in which the glands may be elongated; and such inflammatory changes would, in all probability, gradually decrease or disappear if the animal were permitted to recuperate.

It has been further found that the factor causing malignant tumors in animals is very sensitive to heat, much more so than normal epithelium of the skin. It can, however, be preserved for a considerable time on ice—a fact in itself sufficient to disprove Schüller's views as to the cause of cancer. It is not killed by being placed in a very weak solution of potassium cyanid for forty hours, and probably is not destroyed by being placed in glycerin for twenty-four hours. In all such cases the tumor growth is afterward markedly retarded—a fact which, as Mesnil points out, gives some hope of the possibility of an active immunization. Other results obtained by this method in regard to the structure of tumors cannot be discussed here.

These facts applied at first only to sarcoma in rats. Simultaneously with the latter part of the investigations on sarcoma, however, the well-known Danish pathologist, Jensen, obtained identical results with carcinoma in mice; so that we can safely assume that sarcoma and carcinoma behave, in this respect, in an identical manner. We can, therefore, with great probability, conclude that a blastomyces, or an organism comparable to the tubercle bacillus, or an ultramicroscopic organism living outside of cells, is not the cause of cancer; further, that it is very unlikely that an organism of the size of a Plimmer body is the cause.

These and other results obtained make it also very improbable that the claim of certain investigators, of having produced tumors by injecting organisms, is justified. It is not even likely that their results can be explained by a transplantation of tumor cells which, in my own work, and in the experience of Jensen and others, never succeeded, if a different species of animal was used. It is much more likely that those investigators had to deal with an accidental occurrence of tumors, which is not rare, especially in dogs.

With this experimental method, which is just in the first stage of development, a number of further problems can be approached, and new questions will arise during the progress of the work. Statistic investigations will gradually lead to definite results, and

experimental researches on the reactions and conditions of growth of animal tissues will give us a deeper insight, which, combined with a continued careful microscopic analysis of tumors, will, in all probability, gradually bring us nearer to an understanding of the conditions of normal and pathologic growth. There is no cause, therefore, for a certain pessimistic tendency, noticeable occasionally, as long as there are new fields of investigation open.

December 17, 1903.

A Case of Pancreatic Lithiasis with Atrophy and Lipomatosis of the Pancreas, Associated with Pulmonary Tuberculosis.

GEORGE P. MÜLLER, M.D.

(From the Pathologic Institute of the German Hospital.)

Pancreatic lithiasis, first recognized in the middle of the seventeenth century by Graaf (1667), is not a common affection, and the great majority of the instances noted in the literature have been found at necropsy. The clinical data so far observed has been so insufficient, so inconclusive, that Kinnicutt (*American Journal of the Medical Sciences*, December, 1902, p. 948) in December, 1902, was able to collect but seven cases, one his own, in which a positive diagnosis of the pancreatic calculi was made or suspected during life.

Moynihan, however, in August, 1902 (*Lancet*, August 9, 1902), reported a case *diagnosed* as chronic pancreatitis with calculus, and operated upon successfully, removing a stone from the pancreatic duct measuring about 12 x 5 millimeters. Moynihan remarks that, so far as he could ascertain, there has been only one case of pancreatic calculus (besides his own) treated by operation, that of Mr. Pearce Gould, in February, 1896. Neither of these cases was mentioned by Kinnicutt in his paper. In the same year Leichtenstern operated upon a patient for cholelithiasis without finding any gallstones. The symptoms, those of severe colic, continued, and at a second operation the head of the pancreas was found enlarged. Nothing was done, however, and the patient died. At autopsy the pancreas was riddled with small abscesses and contained numerous calculi.

Pancreatic calculi are composed in great part of calcium phosphate and calcium carbonate, indicating that they are not formed by the precipitation of these salts from the pancreatic secretion, which contains only a small amount of calcium phosphate, none of the carbonate, and which therefore must be altered in quality by some antecedent affection.

Stagnation of the secretion *per se* cannot be held responsible for the calculi, many cases of complete obstruction of the pancreatic duct having been observed without their formation, and experimentally only one investigator (Thiroloix), by the injection of soot, succeeded in producing an artificial lithiasis. It is evident, however, that some change in the quality of the pancreatic juice, together with some alteration of the epithelium of the ducts produced by an ascending infection or a morbid or indurative process in the gland itself, may in certain cases produce these calculi, particularly if an obstruction is present to the free flow of the secretion.

It is interesting to note that diabetes is frequently associated with pancreatic lithiasis, the latter either the result of the disturbed secretion or the cause of an advanced interlobular chronic pancreatitis which, with its implication of the islands of Langerhans, gives the glycosuria.

Carnot, in 1898, called attention to the occasional presence of chronic pancreatitis in tubercular patients and other observers, including Opie, have noted similar findings. No cause for such association has been advanced beyond mere coincidence.

Neither the subjective symptoms as yet observed nor the various tests of the excretions at present used are sufficient to make a positive or even fairly certain diagnosis of occlusion of the pancreatic ducts.

As a result of the obstruction of the pancreatic ducts by the calculi the parenchyma suffers; an interlobular pancreatitis occurs and atrophy of the gland is the result. The acini degenerate and disappear, while the islands remain unaltered until late in the process, when the pancreas, as in Lancereaux's case, was reduced to a fibrous cord with a calculus occluding the duct of Wirsung.

The following case was observed in the German Hospital last spring. For permission to report the case I am indebted to Dr. Kelly. Dr. Wilson has kindly allowed me to use the few clinical notes.

August S., aged sixty years, a storekeeper, was admitted to the German Hospital, March 18, 1903. He was brought from a distance to the hospital, and was in a dying condition when admitted. Neither he nor the relatives with him could give any history of his past or present illness. Physical examination revealed the presence of pulmonary tuberculosis. He complained of some pain in the epigastrium, and to palpation a sense of resistance was determined. The urine showed a trace of albumin, specific gravity 1019, a few hyaline casts, and no sugar. No other examinations were made, and he died on March 21st, three days after admission.

The necropsy, performed by myself, revealed the following:

Tuberculosis of both lungs, double pleurisy with effusion, ascites, parenchymatous nephritis, pancreatic lithiasis, chronic and atrophic pancreatitis, arteriosclerosis of abdominal aorta and most of its branches, especially of the splenic artery.

The lungs were markedly diseased, with cavity formation. The gall-bladder was normal in size, pale in color, with very thin walls and an atrophic condition of the mucous membrane, as though this organ had been, at some previous time, greatly distended. All of the biliary ducts were patulous.

Upon opening the transverse mesocolon the pancreas was observed to be extremely soft and fatty, although the configuration of the gland was fairly well preserved. It was removed, together with a portion of the duodenum, and upon section was found to be a mass of fat, traversed by fine bands of fibrous tissue, bloodvessels, and nerves. The ampulla of Vater was 8 cm. from the pylorus, was normal, as was the opening of the bile-duct. The duct of Wirsung was found completely obstructed, greatly dilated, packed with white calculi and with thickened walls. The ducts leading into the main ducts contained fine concretions for some distance into the pancreas. The opening of the duct of Santorini into the duodenum was found six inches from the pylorus, but could only be probed upward a short distance.

Microscopic sections of the pancreas revealed an entire destruction of the parenchyma of the pancreas, which was replaced by fat, and a nearly unaltered condition of the islands of Langerhans. The latter are in some instances compressed by fibrous tissue. The bloodvessels are very much thickened. *December* 17, 1903.

A Case of Filaria Immitis in the Heart of a Dog.

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PRESENTED BY DAVID RIESMAN, M.D.

The dog from which the specimen here presented was taken showed during the last two months of life the typical clinical picture of cardiac insufficiency. He was an active, well-developed bull terrier. His owner observed first that the dog breathed with difficulty constantly, and that occasionally when trotting along he would fall suddenly to the ground panting for breath. Physical examination revealed cyanosis of the mucous membranes, ascites, and loud and confused heart murmurs.

Head of dog, showing Filaria immitis in right ventricle.

An attempt was made to benefit the condition by digitalis, but without success. Compassion and scientific interest led to the giving of a fatal quantity of chloroform.

AUTOPSY. Considerable fluid in the peritoneum. Chronic passive congestion of abdominal viscera. The heart weighed one hundred and thirty-six grams (slight hypertrophy). The wall of right ventricle was 6 mm. thick; that of the left ventricle 8 mm. thick. The right auricular wall was somewhat thickened also. On opening the right ventricle a mass of round worms are

seen occupying the conus arteriosus, and extending through the pulmonary orifice. A white thrombus is entangled with the worms. By opening the pulmonary artery the worms can be followed into the left branch of the vessel within the lung. Within the lung the mass of worms blocks the artery to such an extent that it is difficult to see how the circulation could have been maintained. Sections of the liver, kidney, and the spleen showed no larvæ of the worms. The bloodvessels were distended with blood. The renal epithelium showed cloudy swelling.

The worms belong to the order nematodes, being the Filaria immitis, or "cruel worm," described by Leidy. The specimens are cylindric, with tapering ends. Their color is white, and their length about 25 cm., width ½ mm. After removal from the body of the dog they discharged enormous numbers of larvæ in the bottle in which they were placed.

It is a common parasite in the East, particularly in China. It has been found only in the right ventricle and pulmonary artery of the dog. Of its extracorporeal existence we know nothing, but its more frequent occurrence in marshy districts suggests that stagnant water gives favorable conditions outside the body of the host. The larvæ can be found in the peripheral circulation during life. They are found in greater numbers at night, as is the case of Filaria sanguinis hominis, but, unlike the latter, they are also found to some extent by day.

Remarks by Dr. Riesman.

In 1850, Leidy,[1] from two specimens preserved in alcohol in the collection of the Academy of Natural Sciences, described this worm under the name of Filaria canis cordis. In 1856[2] two dogs' hearts, containing the filaria, were sent to him from Georgia. One of these hearts he exhibited at a meeting of the Academy of Natural Sciences in January of the same year. In February, in a paper entitled "A Synopsis of Entozoa and Some of Their Ecto-congeners Observed by the Author," Leidy described the parasite under the new name of Filaria immitis. His reasons for selecting the adjective "immitis," which means cruel, are not given; but they were no doubt good, as he was very particular to choose the designations for the many living and fossil animals discovered and described by him, with due regard to derivation and meaning. In

this paper Leidy also stated that he had found the larva of the Filaria in the blood of the dog. The two dogs from which these hearts had been taken, although quite voracious, had been greatly emaciated; they had also been restless when awake and disturbed in sleep.

The cycle of development of the parasite remained hidden for nearly fifty years. The observations of Manson and of his pupil, Low, on Filaria sanguinis hominis, showing that the mosquito is concerned in the transmission of that parasite—a view that had previously been advanced as an hypothesis by Bancroft—led Grassi to suspect that similar conditions might prevail in the case of the canine filaria, and, together with Noè, he succeeded in working out the life-cycle of Filaria immitis.

The larvæ are sucked up from the blood of the dog by mosquitoes, and wander into the malpighian vessels of the insects, where they develop during a period occupying, in the summer months, about ten days. Leaving their cuticle behind them, the parasites then penetrate into the body-cavity of their host, and in one or two days reach the prolongation of this cavity in the labium. When the mosquito stings, the labium, which does not enter the wound, is reflected. The angle, obtuse at first, becomes quite acute as the stylets continue to penetrate into the animal. Eventually a rupture occurs on the dorsal aspect of the reduplicated labium, and through this the larvæ escape into the blood-channels of their new and final host—in the present case the dog. Within the dog the larvæ develop into the adult filaria. The length of time required for this cycle is unknown; but Grassi and Noè found a small young female Filaria immitis in a dog that had, sixteen days previously, been inoculated subcutaneously with filarial larvæ obtained from Anopheles claviger.

The Filaria immitis is bisexual, and, like the other members of the genus Filaridæ, vivipaprous, throwing into the circulation of its host enormous numbers of living embryos. These swarm in the dog's blood, especially at night, although they may be found to some extent also in the daytime. From the female worms themselves outside the body it is possible to obtain eggs as well as larvæ, and I have placed under the microscope a slide showing the granular eggs as well as embryos in all stages of development. The nocturnal swarming of the filarial larvæ in the blood, in the case of

both the human and the canine species, is eminently suited to the nocturnal habits of the mosquitoes.

Grassi[3] found that the Anopheles claviger and other anopheles species, as well as some of the Culicidæ—*e. g.*, Culex penicillaris and, to a less extent, Culex pipiens—can transmit the parasites.

The adult male filaria is from 12 to 18 cm. long, and from 0.7 to 0.9 mm. wide; the female, 25 to 30 cm. long, and 1 to 1.3 mm. wide. The larvæ measure from 0.285 to 0.295 mm. in length, and 0.005 in width. The worms are found principally in the dog, but also in the wolf and in the fox; they are especially common in China and Japan, where 50 per cent. of the canine population harbor the parasites. They also occur in Italy and in North and South America. Their habitat in the canine species is the right heart and the branches of the pulmonary artery, but they may also be found in the venous system.

Braun[4] cites Bowlby as having observed the Filaria immitis in two human subjects; but when I looked up the original reference I was surprised to find that Bowlby[5] had reported his cases as examples of bilharziasis. I cannot understand this apparent error on the part of Braun. There is a strong resemblance between the canine filarial embryos and Filaria nocturna of man, but there are enough points of difference, as pointed out by Magalhães,[6] to prevent confounding.

Dr. Smith has kindly brought a slide of dog's blood showing the embryo filaria, and will make some remarks upon the subject.

References.—1. Leidy, Proc. Acad. Nat. Sciences, 1850-51, vol. v. 118. 2. Ibid., 1856, viii. 2, 55. 3. Grassi and Noè, Centralbl. f. Bakter., Parasit. u. Infect., 1900, xxviii. 652. 4. Braun, Thier. Parasit. des Menschen, Dritte Auflage, p. 262. 5. Bowlby, Lancet, 1889, I., p. 786. 6. Magalhães, Centralb. f. Bakter. u. Parasit., 1892, 511.

Discussion.

Dr. Allen J. Smith said that, thinking that Dr. Riesman probably had only the adult worm, he had brought a slide of dogs' blood containing the larvæ, which had been obtained from an experiment animal in the University of Texas at Galveston, where the parasite was a comparatively common one. The preparation had been made as an ordinary blood smear, fixed in alcohol and ether, and later washed with an eosin solution which had tinted the blood corpuscles and made thus more prominent the unstained embryos by contrast. He remarked that these embryos should be

of some interest to the members because of their similarity to those of the human filaria, differing from the latter mainly in size, being slightly larger, but, like them, of a nematoid shape, with bluntly rounded head end and rather pointed and tapering tail extremity and enclosed in a delicate sac or membrane. Like the human filarial embryos, those of Filaria immitis were apt to be found in the blood of the dog rather in the night than in the day, the difference being observable, however, only in the blood of the periphery, that of the central vessels being constantly occupied by large numbers. This fact had suggested to the speaker that the peculiar variation there and in the case of the Filaria nocturna of man was probably to be sought, not in any special peculiarity of the parasites themselves, but more probably in some varying condition of the host; and he suggested that an important factor might exist in the degree of contraction or dilatation of the peripheral capillaries depending on the tone of the tissues surrounding those channels—that during the night hours, in connection with the general relaxation of rest, the skin capillaries, unsupported by the relaxed tissues, widened, while in the activity of the day the tissues were in more compact tension, and their capillaries narrower in consequence. Recalling the size of these embryos as about the thickness of the diameter of a red blood cell, and many times longer, it might easily be inferred that in the diurnally narrower capillaries of the skin there would be difficulty for the worm with its undulating outline to enter or progress through those channels, which often permitted the red cells to move forward only singly, "in Indian file," while if they were widened nocturnally the same embryos might enter and move with considerably greater facility. It might be thought of the diurnal appearance of the embryos of the Filaria diurna that probably some minute difference in size of the larvæ existed, making their presence in the tonically narrow peripheral circulation possible.

It should be recalled that in the blood of the dog another filarial embryo was occasionally found, the so-called "hematozoon of Lewis," the larval form of the concealed filaria, Filaria recondita, the adult of which had been found but a single time, then embedded in the fixed tissues of the host.

The speaker referred also to the fact that the adult presented by Dr. Riesman was to be met not only in the right heart, as was usually the case, or in the pulmonary vessels, as in the specimen

before the Society, but that it had been encountered in the two cavæ, in the iliac and femoral veins, rarely in the arteries, and even in the fixed tissues of the host, as in the serous membranes and in the subcutaneous tissue.

Dr. Daland said that he had a dog's heart filled with the worms and hoped to show it on some future occasion.

Dr. McFarland said that he could not understand Dr. Smith's explanation of the disappearance of the filaria from the blood during the day. Seeing the immense number of parasites in the blood, their stoppage in the peripheral capillaries should obstruct the circulation by parasitic capillary emboli. Further, in the course of some hours, their lodgement in the capillaries should filter them out of the blood so that that of the great vessels would gradually become empty of them.

Dr. Smith, in answer to Dr. McFarland's objection that parasitic embolism should frequently follow if the mechanic idea above mentioned were true, replied that the objection might easily be set aside in that probably no important results would follow lodgement of the embryonic worms in the capillaries, since the capillary circulation was so freely anastomotic, and the lodgement was likely to be only temporary (namely, until nocturnal relaxation again followed); further, that if the embryos were once in the capillaries in question exit should be at least as easy through the progressively enlarging channels into the veins as was entrance from the arteries to the place of greatest narrowness of the capillaries, and for such reason it might be thought that many of the parasites present in the capillaries at the time of resumption of tone in the hours of activity might make their way out of the capillary plexus into the veins, although further entrance for the time from the arterial side of the circulation into the capillaries was suspended. It might be added to the above that if the parasites be held in the narrow capillaries at time of puncture of the skin and withdrawal of blood during the day, they could not easily be carried with the current out into the drop of extracted blood, while the same puncture might at night with the freer current in the capillaries be a means of withdrawal of numerous embryos if they were moving more freely through the channels punctured—thus making their absence from the peripheral circulation only an apparent and not a real absence.

March 10, 1904.

Proceedings

of the

Pathological Society of Philadelphia.

April, 1904. New Series, Vol. VII., No. 4.

TABLE OF CONTENTS.

Rosenberger, A Resume of Literature Relating to Serum Diagnosis.—McConnell, Sarcoma of the Bladder and Prostate Gland Causing a Cyst of the Urachus and Bilateral Hydronephrosis in a Nine-months-old Baby.—Randolph, A Case of Spontaneous Arrest of Growth in an Endothelioma, with Subsequent Inflammatory Absorption.

A Resume of Literature Relating to Serum Diagnosis.*

RANDLE C. ROSENBERGER, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

It is not the writer's purpose to attempt an exhaustive review of all the literature bearing upon this interesting subject, but to include so far as possible the most recent progress in serum diagnosis.

As is well known, the first application of serum reaction to diagnosis was in enteric fever. Ross claims that the discovery should be accredited to Grünbaum, who in 1896, while working in Gruber's laboratory, in Vienna, obtained positive agglutinative reactions in typhoid fever. The first test was made on March 14th. This discovery was promptly corroborated and quickly followed by other investigators obtaining agglutinative reactions in other diseases and with other bacteria. As examples of the widespread application of the test the following organisms are now agglutinated by the serum in their selective cases: The Streptococcus pyogenes, diplococcus of pneumonia, bacillus of plague, colon bacillus, bacillus of dysentery (Shiga), paratyphoid bacillus, paracolon bacillus, Gärtner's bacillus, Booker's bacillus, staphylococci, gonococcus, spirilla of cholera and of relapsing fever, bacillus of tuberculosis, members of the proteus group, bacillus of tetanus, Oidium lactis, bacillus of diphtheria, and others. Not only are bacteria subject to this reaction, but animal parasites, as the

* Read by invitation.

trypanosoma, have been agglutinated by the serum of patients suffering from sleeping sickness and trypanosomiasis fever.

Preyer[1] claims that the blood of all native Indians possesses agglutinating power in health, but this statement is contradicted by W. C. Brown,[2] who made a number of tests with negative results.

Technic. The technic of the Widal test is perfectly simple, and usually consists in bringing together the bacilli in young bouillon culture or a water suspension from an agar culture and the serum of the individual in a proper dilution. The culture should not be over twenty-four hours' old, and the bacilli actively motile, although dead typhoid bacilli may also be used for the reaction. Examine the culture before beginning the test, to see that clumps are not present. If they exist the culture should be filtered through paper and the filtrate used for the test. The blood or serum may be collected in various ways: (1) by a capillary pipet in which coagulation and separation occur; (3) by the white blood cell pipet, in which a dilution of 1 : 20 is made; (3) obtain pure serum from a blister; (4) dried blood may be used.

The technic employed at the Jefferson and Philadelphia Hospitals is the use of a nonincubated bouillon culture of the typhoid bacillus not over twenty-four hours' old, mixing one drop of this culture with one drop of diluted blood. The dilution of the blood, 1 : 20, is facilitated by means of the pipet used for counting leukocytes; using a drop of each a dilution of 1 : 40 is obtained; thirty minutes is given as the time limit.

Haedke[3] recommends the mixture of a loop of solid culture with typhoid serum on a glass slide; McWeeney[4] by mixing 1 per cent. serum in a hanging drop with bouillon culture and placing in the incubator at 37° C. for four hours; twisted and convoluted chains of motionless bacilli will form if the case is one of enteric fever.

Where a test is made with dried blood it must be moistened with distilled water, the difficulty of obtaining an accurate dilution being one objection to this method. There is much difference of opinion as to just how much the serum should be diluted. Most observers recommend a dilution of 1 : 20 or 1 : 40; some use 1 : 200, and even 1 : 20,000 has been found effective in an occasional case. It has been found very often that the reaction is

negative with dilution of 1 : 20, and positive with dilution of 1 : 50, and vice versa. This apparently is accounted for by the presence of certain bodies—proagglutinoids, described by Shiga[5]—that develop from the agglutinins and combine with the bacilli, but lose the power of combining with the agglutinin. These bodies—proagglutinoids—are developed from the agglutinins through extraneous influences, and possess a greater affinity for the bacilli than the unchanged agglutinins, having lost their agglutinophore group, but retaining the haptophore group; they have been produced artificially by heating dysentery-immune serum to 60° C., or by shaking with chloroform, or exposing it to sunlight for a few days (Eisenberg and Bail). Coleman and Buxton[6] insist upon a dilution of 1 : 50.

J. S. Billings, Jr., uses a dilution of 1 : 20; clumping and death of the bacilli must occur in ten minutes.

Bryant[7] says that in Guy's Hospital it is customary to use 50 per cent., 5 per cent. and 0.5 per cent. dilution, and Widal's reaction is not considered positive unless clumping and immobility of the bacilli occur with the 1 : 200 dilution within half an hour. Examinations made before the eleventh day of the disease with a negative result are of little value. In this connection he mentions W. C. C. Pake's analysis of 304 consecutive cases in which the error was only 3.03 per cent.

Baltharde[8] states that by the injection of nonfatal doses of the typhoid toxin an antityphoid serum possessing agglutinating power of 1 : 100,000, but without decided bactericidal action (in vitro), may be obtained.

Libman[9] claims that if the blood is employed immediately after drying the result is not so good as when it is used some hours later. However, in the summer, if the blood is not taken for the test within twenty-four hours it is not so easy to obtain the Widal reaction.

Ficker[10] has perfected a fluid to which he has applied the name diagnosticum, with which it is possible to obtain the Widal reaction without the necessity of living cultures of typhoid bacilli. The fluid is sterile, slightly turbid, and is said to keep well for nine months. The reaction is perceptible to the naked eye, absolutely unmistakable, and occurs at ordinary room temperature. "The fluid is derived from one and the same typhoid stem."

A. J. Wolff[11] recommends smearing an agar slant with typhoid feces and from the growth resulting inoculate one or two tubes of bouillon. The bouillon must react from 1 to 2 per cent. alkaline with $\frac{N}{10}$ acid, using phenolphthalein as indicator. A sample of the blood is taken and mixed with the bouillon culture and placed under the microscope. If there is sufficient agglutinative material present the typhoid bacilli will clump while the colon bacilli remain active. In thirty-five tests thus made, every case that gave a positive reaction by this method proved to be typhoid fever.

Proescher[12] recommends collecting the blood in U-shaped tubes of a diameter of 2 mm. The tubes are closed, centrifugalized, and the serum separated by breaking the tube with a file. The serum is then transferred by capillarity from the tubes to pipets graduated in 0.1 c.c. This is then diluted in 1 : 10 normal salt solution, and portions are placed in small test tubes, the first part without additional dilution, the second diluted one-half, and so on through five dilutions. Each tube then receives 5 c.c. of typhoid bouillon culture which after twenty-four hours' growth has been killed by adding 1 per cent. formalin. This diluted culture is then added to the tube in quantity equal to that the tubes already contain. The tubes are at once emptied into small glass dishes and placed in the incubator for one to two hours. After this they are examined with relatively low powers (about 50 diameters), when the agglutinative masses can readily be seen.

The reaction occurs by the methods just given, in from fifteen minutes to two hours, while in the macroscopic test, where a small tube of the culture has added to it the blood or serum of the case, five or six hours are necessary for the reaction to be completed.

In the microscopic test a positive reaction is said to occur when all the organisms in the field group or agglutinate and motility ceases. In the macroscopic or tube test a positive reaction is said to occur when the uniform turbidity clears and the bacteria settle in small masses at the bottom of the tube.

A. E. Wright[13] in the case of patients suffering from or preventively inoculated against tuberculosis uses a suspension of extremely fine detritus of tubercle bacilli in carbolized water. By employing 1 : 1000 solution of common salt to dilute the serum, instead of 8.5 per 1000 solution prescribed by Koch, fallacious agglutinations and precipitations are completely avoided.

Wright's modification of Koch's procedure is as follows: A minute quantity of powdered tubercle bacilli is placed in an agate mortar, to which is added, drop by drop, a 0 5 per cent. solution of carbolic acid. After triturating for a few minutes the turbid suspension is siphoned into a capsule. After sealing the ends of the capsule it is centrifugalized and the supernatant milky fluid, which separates in a few minutes, is used for the test. The blood is obtained in a special capsule, which is then placed in a centrifuge until the serum separates from the cellular elements. A capillary pipet is then used, and into this is aspirated one volume of the undiluted serum and one volume of the test fluid above described. This mixture is expelled, and after thoroughly mixing upon an ordinary microscopic slide exactly one volume is reaspirated into the stem of the pipet.

Having divided off with a suitable bubble of air, there is introduced into the stem of the pipet one volume each of serum and of the inert diluent (1 : 1000 solution of chlorid of sodium). These two last-mentioned volumes are again expelled, and, after mixing, constitute the quantity of diluted serum for our second test dilution. Having mixed this on a slide, the mixture is again reaspirated, and as in the former case and all subsequent dilutions, using exactly one volume of the mixed fluids. Another serum dilution is now made, employing for this purpose a full volume each of twofold dilution of serum and of the inert diluent. We then fill upon these principles in succession (into the stem of our pipet) a series, ordinarily seven or eight graduated dilutions of serum mixed in each case with a precisely equivalent volume of the bacterial suspension. Completion of these series is reached by introducing into the pipet a mixture of equal volumes of the inert diluent and test fluid to serve as a control. The pipets are then sealed and placed upright in the incubator or on the laboratory bench. After an interval of twelve hours flocculation and deposition associated with a corresponding clearing of the supernatant fluid takes place. The precipitate in the twofold dilution is in most cases—presumably as a consequence of bacteriolysis—markedly less in bulk than the precipitate in the succeeding dilution. After standing for a long time a deposit makes its appearance also in the higher dilutions of the serum and in the control.

Besides tuberculosis this method is also useful in those suffer-

ing from or preventively inoculated against typhoid and Malta fevers.

Romberg[14] recommends mixing a dry culture of tubercle bacilli with one liter of bouillon containing five grams of carbolic acid. For use one part of this is mixed with three parts of distilled water. One part of serum extracted by wet cups is added to 5, 10, 15, or 20 of the emulsion which is left in the tubes. If at the end of twenty-four hours this becomes clear the reaction is considered positive. The test is not entirely reliable.

Koppen[15] treats the tubercle bacilli with caustic potash solution, thus saponifying them. The stem fluid which he uses for the agglutination test is milky and homogeneous and does not become putrid. After this saponification the tubercle bacilli take the stain as readily as before.

Thellung[16] finds that the agglutinins can be produced by the injection of tubercle bacilli into guinea-pigs and rabbits. It is also claimed that the agglutination does not occur constantly or regularly in tuberculosis.

Lagriffoul[17] in the serum diagnosis of tuberculosis adopts the technic of Arloing and Courmont. The cultures are made in a 2 per cent. peptone medium containing 8 per cent. glycerin. This medium is reinoculated every twenty days, and incubated at 30° C., with agitation once daily. Macroscopically the test was facilitated with dilutions of 1 : 5, 1 : 10, and 1 : 15.

Loeb[18] uses an eight- to twelve-day old culture of the tubercle bacillus previously grown on potato and homogenized. To this is added clear blood serum or serous effusion in the proportion of 1 : 5 or more. This is followed, if the reaction is positive, by a flocculent precipitate in the course of six hours.

Neufeld[19] studied the agglutinative action of the serum of immunized animals on cultures of the pneumococcus in broth by the usual methods, and was thus the first to note typical agglutination reactions in various dilutions, both microscopically and macroscopically. In dilutions of 1 : 50 he was able to obtain the reaction in from fifteen to thirty minutes.

Bezançon and Griffon[20] inoculated 1 to 2 c.c. of clear undiluted serum with pneumococci and observed the appearance of the growth, at the end of fifteen or sixteen hours' incubation, to be characterized by the formation of a membrane at the bottom of

the tube. This membrane consisted of branches and chains of pneumococci; this so-called agglutination can be observed by the unaided eye. These two observers then applied the method to 186 patients, among these being 64 of undoubted pneumococcus infection. In the serum from these cases the growth in bunches and chains was observed easily and constantly. The dilutions used were 1 : 50; they found that the results were very uncertain.

Weaver[21] in testing the agglutination reaction in scarlet-fever patients and others used cultures of the streptococcus in bouillon which was neutral to litmus and 1 per cent. acid phenolphthalein. The blood was obtained from a vein of the arm and serum allowed to separate from the clot in the ice-box. The serum was diluted with the same bouillon as used for the culture in strengths of 0.5, 0.25, and 0.125; by means of pipets of uniform size one part of these various strengths was added to thirty parts of the twenty-four hours' bouillon culture. The mixtures of serum and culture were then placed in small test tubes, each containing about 1 c.c., kept at room temperature and examined. If a positive agglutination reaction took place a sediment formed at the bottom of the tube, made up of flakes and granules which would not break up upon agitation. The agglutination takes place more rapidly in the incubator than at room temperature, often being complete in one hour, and usually in three to five hours; at ordinary room temperature agglutination took place in eighteen to twenty-four hours.

Wadsworth[22] in the agglutination tests in cases of pneumococcus infection in man and animals uses a peptone broth made from meat infusion which has been carefully neutralized before boiling. In a flask containing 200 c.c. of this medium the maximum growth of the pneumococcus was evident in twenty-four or thirty-six hours. At this stage the culture was centrifugalized, the clear fluid decanted, and the sediment shaken with about 15 c.c. of isotonic (0.85 per cent.) salt solution. This left a dense, finely divided suspension of pneumococci, less than forty-eight hours old. Dilutions with the sera to be studied were then made in small, slender tubes and observed for some twelve to eighteen hours at 37° C. The more marked reactions may be complete in five or six hours or less, but twelve or more hours are often required to bring out the more delicate tests. Sera stored in the ice-box were found to be active for four or more months; the lytic power was gone,

and the agglutination did not appear in high dilution; but in low dilutions immediate and complete reactions took place.

The normal serum of the rabbit always failed to agglutinate the pneumococcus cells. This was also the case with the serum of the cat and dog. Normal bullock's serum, however, gave some very marked agglutinations even in dilutions of 1 : 50. Ascitic fluids tested also failed to agglutinate in dilutions of 1 : 5 and 1 : 15, but normal sera (human) gave reactions in dilution up to 1 : 10 in less than eighteen hours; 1 : 30 failed to agglutinate. In three cases of lobar pneumonia positive reactions were obtained in dilutions of 1 : 10 after five hours' incubation.

Cairns[23] insists upon a perfectly homogeneous culture of the Bacillus pestis for the serum diagnosis of the disease. For the reaction he uses a small test tube 9 cm. in length and 0.7 cm. internal diameter, into which a drop of the blood serum (collected in a small Pasteur pipet) is placed, and then the culture of the organism up to the required dilution. The cultures are prepared by taking a twenty-four or thirty-six hour incubated growth upon agar, and filling with 0.75 per cent. sterilized salt solution to cover the solid medium. The growth was then, as far as possible, transferred to the salt solution by rubbing the surface of the agar with the blunt end of a Pasteur pipet. These emulsions were then set aside in a sterile test tube for a short time, to allow any cohering masses to settle. A too concentrated emulsion is agglutinated very slowly and often very imperfectly; while the exact degree of dilution is undoubtedly a matter of some importance, it can only be determined after considerable experience in agglutinative work. The tubes are then set aside, and when complete sedimentation occurs—eighteen to twenty-four hours—a positive reaction is recorded.

Klein[24] in preparing a homogeneous culture of the Bacillus pestis for the agglutinative reaction used a gelatin culture distributed in a 0.75 per cent. physiologic salt solution. His reason for using a gelatin culture is that, in his opinion, the surface colonies upon this medium are less viscid and dryer than those upon agar. "If to a good salt emulsion of plague bacilli—taken from the gelatin surface—bouillon is added in the proportion of one of bouillon to twenty of emulsion, the result of positive agglutination is evident in from twelve to fifteen minutes." Experiments were

then made with blood of rats that had been injected first with Haffkine's prophylactic, then with small doses and finally larger doses of living plague organisms. Klein found that in several animals thus treated, three and five weeks after recovery agglutination took place in dilutions of 1 : 20 and 1 : 40 in ten minutes.

McFadyean[25] showed that the serum of glandered horses possessed the power of agglutinating glanders bacilli. In the great majority of cases of glanders a 1 : 50 dilution of the serum produces marked agglutination in a few minutes, while in that of nonglandered animals no effect is produced under these conditions. He finds that a more delicate and reliable method is to grow the bacillus in bouillon containing a small proportion of the serum to be tested. In this way he has obtained a distinct sedimenting action with a serum which did not agglutinate at all distinctly in the ordinary method.

Heanley,[25a] in testing the sedimentation and agglutination reaction in cases of glanders, used 1 part of glanders serum diluted with 109 parts of normal salt solution, and 110 parts of emulsion of glanders bacilli in normal salt solution. The same procedure was adopted with two samples of serum from diphtheria patients. When examined, in ten hours, the glanders specimen showed definite sedimentation, the others did not. A repetition of the experiment gave the same result, and a dilution of 1 : 505 also proved positive; typhoid and normal serum showed no sedimentation.

The glanders serum could be differentiated from the others in about four hours, but the reaction became more obvious later. Eleven tubes containing blood were numbered, and included blood from one normal person, two from enteric fever patients, two cases of scarlet fever, two of glanders, one of tuberculosis, one of scarlet fever with diphtheria, and two cases of diphtheria. Dilutions of 1 in 505 were made, and only the two glanders specimens gave the reaction. In another experiment samples of blood from two cases of enteric fever, three of scarlet fever, two of diphtheria, two of variola, two of glanders, and two specimens of normal blood were examined in dilutions of 1 in 220, and four tubes showed sedimentation. Dilutions of 1 in 505 were then made, and all showed sedimentation. These four cases included two cases of glanders, one of variola, and one of scarlet fever. With

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dilutions of 1 in 2500 only the glanders cases produced sedimentation. In the microscopic agglutination test an emulsion of bacilli was made from a growth on sloped glycerin agar by half filling the tube with previously boiled salt solution and gently agitating for a few minutes. In one series of observations a thirty-six hour culture was used, and the serum and emulsion were mixed on a slide and covered by a cover-glass. Serum from a case of glanders of six-months' duration was diluted with nine times its volume of normal salt solution, and then ten of bacterial emulsion were added, making a dilution of 1 in 20. Serum of two cases of diphtheria were treated in the same way. It was found that in mixtures containing the serum of the diphtheria patients clumping was marked, while in the preparation containing the glanders serum more bacilli were free than clumped. In using diphtheria antitoxin as the diluent of cultures, clumps were also quickly and completely formed.

Typhoid. In typhoid fever the reaction sometimes is absent throughout, and this may be due to a too high dilution; therefore, a low dilution, 1 : 20, or 1 : 10 in some cases, should be used. Curselmann[26] claims that the reaction takes place only in the minority of cases before the termination of the first week; most frequently not until the second week, while rarely it is delayed beyond that time. Complete absence of the reaction is one of the rarest exceptions. Kennedy[27] claims that Widal's reaction may be present as early as the fourth day, and may be continuously or intermittently present throughout the disease, or in unfavorable cases it may be absent altogether in the first few days. To obtain the full value of the reaction, tridaily tests should be made throughout the disease.

In 165 cases of enteric fever, Libman[28] obtained a positive reaction with 1 : 30 and 1 : 50 dilutions in 137 cases. In some instances as many as sixteen days elapsed before the reaction was positive in 1 : 50, and in eight cases that were positive in 1 : 20 there was no reaction in a dilution of 1 : 50. He claims that it is essential in performing the test that at least two dilutions should be made—1 : 20 and 1 : 50.

Cabot,[29] in a collated series comprising 5978 cases of enteric fever, has found that a positive reaction occurred in 5814 or 97.2 per cent., while in 5668 control cases a positive reaction occurred

in 323, or 6 per cent. Gwyn and Block in 151 cases of enteric fever obtained a positive reaction in 144. In four cases it developed on the 22d, 26th, 35th, and 42d days respectively. In only 26 cases was the reaction present before the seventh day of the disease. Stengel and Kneass[30] in 2392 collated cases of enteric fever found that a positive reaction was obtained in 2283 and negative in 109 cases. Coleman and Buxton[31] state that Brill found that of 4879 cases of typhoid the Widal reaction occurred in 4781, or 97.9 per cent. The reaction is absent in paracolon infection.

S. S. Adams[32] reports that of 70 cases of enteric fever in which the Widal test was made, 50 gave positive reactions. Widal[33] states that the agglutination reaction fails in 1 case out of every 40 of enteric fever. He has seen it as early as the third day. The most reliable results are obtained during the second week. It may be positive in dilution of 1 : 8000.

Allaria and Bozzolo[34] show that the Bacillus typhosus may be recovered from the spleen and other organs of the newborn at autopsy, when before death the Widal reaction was negative. In 4 out of 11 cases a positive reaction was obtained at varying days following birth. In 2 cases placental blood gave a positive and the blood of the newborn a negative reaction.

J. S. Billings,[35] in 1908 specimens of blood examined during 1901 by the Board of Health, found that 304 showed a positive reaction, and 111 cases were considered typhoid clinically, although the blood was doubtful or negative. In 131 cases where the reaction was doubtful, and in 1362 where it was negative, the cases proved not to be typhoid. In a large number of the positive cases the reaction was not obtained until the seventh or eighth day. In a comparatively large number several examinations were made with negative results, and yet the autopsy showed the correctness of the clinical diagnosis. It, therefore, follows that although a positive reaction may be taken as meaning typhoid with almost absolute certainty, yet a negative result does not by any means preclude the possibility of typhoid, and demands that another specimen be sent if the clinical signs persist.

Libman,[36] in 3514 tests in 816 cases, comes to the conclusion that the Widal reaction when positive always means the presence or preexistence of typhoid. Partial reaction should be negative, and a negative reaction does not exclude the existence of typhoid.

Wilson,[37] in a study covering 1650 blood examinations for the Widal reaction, states that less than 7 per cent. are what might be called partial or incomplete. They occur with much greater frequency in tuberculosis and malaria than in typhoid.

Wright and Semple[38] report 18 cases of enteric fever in which, after subcutaneous injections of 1 c.c. of sterilized cultures of the Bacillus typhosus, the blood of the patients caused arrest of motility and agglutination of bacilli, as seen in Widal's reaction.

McFarland and Anders[39] in reporting 230 cases of enteric fever obtained positive reactions in 219, or 95.64 per cent. Of these 219 cases 128 showed the reaction before the eighth day, 36 during the second week, 45 between the seventeenth and twenty-first days, 8 not until the twenty-fifth, and 2 as late as the twenty-eighth-day.

Vickery[40] obtained a positive Widal reaction in 41 out of 59 cases of enteric fever.

Sears[41] in 205 cases of typhoid fever obtained the Widal reaction in 168 and negative results in 33.

Ruediger[42] in 30 cases of enteric fever obtained a positive Widal reaction in 26 cases.

Elsberg[43] in 36 cases of enteric fever found the reaction present in 8 cases one month after convalescence.

Hektoen,[44] in 2 cases of typhoid fever which were at first confounded with scarlet fever, obtained pure cultures of the typhoid bacillus from the blood which in each case was agglutinated by the serum of the patient.

Thacher[45] cites an "observer who had applied the Widal test in 334 cases. He found it present in only 6 per cent. at the end of the first week, in 36 per cent. at the end of the second week, 67 per cent. at the end of the third week, and 94 per cent. on the thirtieth day."

Dun[46] reports a case of typhoid fatal on the thirteenth day. The Widal reaction was absent on the eleventh and twelfth days. He mentions that Wright (Glasgow) has observed that in severe cases the reaction is frequently absent.

Haim,[47] in a case of typhoid fever, isolated from the stools the Bacillus proteus vulgaris that was agglutinated by the serum of the patient in dilution of 1 : 50. Widal reaction was also positive in dilution of 1 : 50.

Harrington[48] during an epidemic of typhoid fever, of 90 cases in which the Widal test was performed, 58 were positive, 25 negative, and 7 unsatisfactory for "various reasons." In some of these two or three examinations were necessary before a positive reaction was obtained.

Pallard[49] has shown that in typhoid spine (spondylitis typhosa of Quincke, 1899) the Widal reaction becomes more marked and increases with the augmentation of the spinal symptoms. He concludes that the condition is an osteomyelitis due to the Eberth bacillus.

Carr and Roughton[50] report a case of sapremia in which, in the first days of the disease, a positive Widal reaction was obtained, but which after six weeks failed to give the reaction.

The writer contributes 134 cases of enteric fever, of which 109 gave positive and 25 negative reactions. In 153 cases other than enteric fever a positive reaction was obtained in 4 cases each of influenza and pleurisy, 1 each of malaria, peritonitis, parotitis and pneumonia. A number of cases of typhoid fever where a negative reaction was obtained were diagnosed as "abortive typhoid."

Browne and Crompton[51] state that Widal in the examination of 40 cases of typhoid found 11 that gave the reaction long after convalescence. One reacted eight and a half years after with a dilution of 1 : 18,000. Browne and Crompton examined 68 cases from one to forty-eight months after the attack. Only 3 gave positive reactions in dilutions of 1 : 20 or 1 : 50. One of these was a case of biliary calculi, and they think that the late reaction was due to the persistence of the bacillus in the gall-bladder.

Fison[52] in 21 cases found 18 that gave a positive reaction from three months to eight years later. Dilutions used were 1 : 2, 1 : 9, in thirty minutes.

Renard[53] in 104 cases of enteric fever obtained a positive reaction in 35, 5 of these being twenty years after the attack. Dilutions were 1 : 10.

Stern and S. Klower[54] in 100 persons ill with diseases other than typhoid fever obtained a positive Widal reaction with the typhoid bacillus in 25 cases, with a dilution of 1 : 10 : in 10 with a dilution of 1 : 20; 2 in which a dilution of 1 : 30 was used, and 1 in which a positive reaction occurred in dilution of 1 : 40.

Lagriffoul[55] in cases of divers affections, including bronchi-

ectasis, brown induration of the lung, syphilis, osteosarcoma of the knee, neurasthenia, disseminated sclerosis, pneumonia of the aged, and 1 case of typhoid fever, found the Widal reaction negative. The reaction was positive, however, in 9 cases of typhoid, 1 case each of articular rheumatism, enteritis, syphilitic fever, and hemichorea.

Zupnik[56] obtained a positive Widal reaction in 4 of 6 cases of Weil's disease, 6 of cholelithiasis, 1 of cholangitis, 1 of carcinoma of the liver, all of which were complicated by icterus.

Eckardt[57] records 2 cases of Weil's disease in which the blood gave the Widal reaction with the typhoid bacillus in dilutions of 1 : 1000 after two hours.

Joachim,[60] in a patient suffering from purulent cholangitis and one of carcinoma of the ductus choledochus, obtained a positive agglutination reaction with the Bacillus typhosus, cholera spirillum and Bacillus pyocyaneus. In the latter case the test failed in high dilution, while it was positive in the first case in dilution of 1 : 50.

Koehler[61] in 10 cases of disease of the liver, of which 8 were icteric, found an agglutination with the typhoid bacillus present in 6. The highest dilution employed was 1 : 50, although 1 : 40 was generally used, and once 1 : 10.

Magele[62] reports an abscess of the liver with positive Widal reaction in dilution of 1 : 100. At the autopsy the findings excluded typhoid. The positive Widal reaction was attributed to the bile in the blood.

Libman[63] claims that the presence of jaundice, leading to a positive Widal reaction, is far from being convincing, as no effort had been made by bacteriologic examinations to determine whether or not typhoid bacilli were present in the gall-bladder, feces, or urine. Even with dilutions of 1 : 1 he had not obtained any characteristic reaction. In only 4 cases had he obtained a positive Widal reaction in the presence of jaundice.

Koeningstein,[64] using mixed cultures of the Bacillus typhosus, colon bacillus and cholera spirillum with gall (taken from cadavers under sterile precautions) in dilutions of 1 : 10, to 1 : 100, found that in 21 tests there was no positive agglutination reaction; in 2 a partial reaction occurred. He injected two dogs with small amounts of a hemolytic poison, which resulted in the production of icterus. The serum before the jaundice developed gave a nega-

tive reaction in one dog, while in the second animal a positive reaction occurred in dilution of 1 : 10. The results remained the same after the development of jaundice. Tests made with the serum from patients affected with icterus gave negative results in 7 cases, using the typhoid bacillus. In one case agglutination of the colon bacillus was obtained.

Cantani[65] reports experiments to determine the agglutinating power of bile from normal animals and from those immunized against different bacteria. Bile from normal dogs, guinea-pigs, oxen, and rabbits did not agglutinate the Bacillus coli communis, Bacillus typhosus, Bacillus influenzæ, staphylococcus and streptococci. The bile from animals inoculated with these organisms failed to cause agglutination during the stage of acute infection. On the other hand, where bile from animals highly immunized against a specific organism was used agglutination occurred rapidly and in high dilutions. The agglutinating power of the bile never exceeded or even reached that of the serum. From these observations the author concludes that if agglutinins are present in the serum in small amount they do not appear in the bile, and when in great quantity in the blood they may then pass over into the bile.

Pneumococcus. Rosenow[66] obtained agglutination with the pneumococcus in 77 out 83 cases of pneumonia (croupous).

Ludwig Jehle[67] in 6 cases of pneumonia came to the conclusion that in all the cases that end by crisis there was present a relatively high degree of agglutinating power in the serum. The power of the agglutination appears at the beginning of the disease and remains to the onset of the crisis. After crisis there is a rapid diminution in the agglutinating power, so that in forty-eight hours it is present only to a slight degree, and in four days has entirely disappeared. He suggests that the test may be of diagnostic value in the early stages of pneumonia in doubtful cases.

Huber[68] studied the agglutination of the pneumococcus with the serum of patients having pneumonia. The reaction could be obtained about the fifth day, and remained until the crisis.

Tuberculosis. Arloing and Courmont in 191 clinically tuberculous patients obtained a positive agglutination in 87.9 per cent.; 12.1 per cent. did not give the reaction. Of 130 clinical non-

tuberculous, 34.6 per cent. reacted, 85.4 per cent. did not. Of 41 healthy individuals 28.6 per cent. reacted. 73.2 per cent. did not. Loeb personally examined 52 cases in which the technic of Arloing and Courmont was followed. His results are as follows: (1) Cases in which blood sera were used: *a*. Nontuberculous. 2— (100 per cent.), 0—. (2) Cases in which serous effusions were employed: *a*. Nontuberculous. 6— (30 per cent.). 14— (70 per cent.). *b*. Tuberculous. 12 — (72 per cent.). 4— (27 per cent.). In 15 cases of pulmonary tuberculosis most of them with bacilli in the sputum, 13 reacted and 2 did not. (Lagriffoul). Four of the former were quite cachectic; of these 2 gave the reaction, while in the other 2 the reaction was negative. In 5 cases of surgical tuberculosis all reacted. In 10 cases of pleural effusion all were positive with blood serum. In 5 the serum of the effusion was used, and 4 reacted positively and 1 negatively. In 1 case the serous fluid was negative and the blood serum positive.

Lagriffoul and Pages[69] claim that the serum of a newborn child of a tuberculous mother does not generally agglutinate the tubercle bacillus. If the agglutinative substance exists in abundance in the blood of the mother a certain quantity may enter the fetal organism.

Marchetti and Stefanelli[70] conclude from researches in tuberculosis that the serum reaction applied according to the method of Arloing and Courmount is positive within the first six hours in 43 per cent. of cases. In incipient or light cases it gives positive results in 88 per cent. In cases of lupus the reaction was negative, as it was in 9 cases out of 10 in which no clinical symptoms of tuberculosis were present. It should be relied upon as a test only when the reaction occurs during the first six hours, as in cases other than tuberculosis the reaction may take place after this time.

Dysentery. Wollstein[71] found the Shiga bacillus in 39 out of 114 cases of summer diarrhea of infants. The organisms reacted in 21 cases to the Flexner (Manila) serum in dilutions of from 1 : 50, and 1 : 3000, while Shiga serum gave the agglutination test in dilutions up to 1 : 200. The serum reaction is uncertain during the first week, frequently positive after the sixth day, but may be absent for two weeks. It cannot be relied upon for early diagnostic purposes in infants and young children.

Rosenthal,[72] in 30 cases of dysentery occurring in Moscow, found the reaction absent during the first week, strong from the tenth to twelfth day, and less intense after the fourth week. Fifty-two days was the latest time in which he was able to obtain an agglutination.

Strong[73] isolated a bacillus from cases of dysentery in Manila, and tested the serum of 100 individuals, some of whom were suffering from various disorders. In 2 a previous history of dysentery was obtained, and 12 were healthy. In all these cases a dilution of 1 : 10 was employed, and a time-limit of thirty minutes given. A positive reaction occurred in one surgical case and a partial reaction with one specimen of normal blood.

Leonard Rogers[74] found in cases of dysentery that the serum reaction was present from the sixth day on, but least marked under ten days.

Duval and Bassett[75] in 43 typical cases of summer diarrhea in infants succeeded in isolating the bacillus dysenteriæ (Shiga). The organisms were agglutinated by the blood serum of patients from whom they were secured, the serum of other infants suffering with summer diarrhea, the serum of patients with acute dysentery, and with antidysenteric immune serum, but not with the blood serum of healthy children.

Park and Dunham[76] examined 22 cases of dysentery occurring in different localities, and obtained a positive agglutination reaction in 12 cases in dilutions of 1 : 50.

Doerr[77] in an epidemic of dysentery occurring in an Austrian town (Bruck) observed 168 cases. The bacillus isolated by the author was agglutinated always by the serum of convalescents from the disease, in dilutions of 1 : 50; some dilutions were used 1 : 200. The serums of individuals from whom the bacilli were isolated did not seem to agglutinate the bacilli any more or less than heterologous serums.

Lawrence B. Pilsbury,[78] in an article upon the agglutination of dysentery bacilli by the blood of noninfected persons, examined 114 cases of diseases other than dysentery. He obtained a positive agglutinating reaction varying from "complete" to "slight" with the bacillus of Shiga in 108 cases in dilutions of 1 : 10; in 93 cases in dilutions of 1 : 20; in 71 cases in dilutions of 1 : 50, and in 29 cases in dilutions of 1 : 100. With Flexner's bacillus agglu-

tination occurred in 93 cases in dilutions of 1 : 10; in 72 cases 1 : 20 dilutions; in 33 cases, dilution 1 : 50, and in 15 cases with dilutions of 1 : 100. The term "complete" was applied only to those reactions where no free bacilli were seen and the clumps were large; "good" was applied to those reactions where small clumps occurred and a few free bacilli. This reaction was especially seen in dilutions of 1 : 20. "Fair" agglutination was applied to those showing fairly good clumps and where a great many free bacilli retained their Brownian movement to a considerable degree. A "slight" reaction implied one which showed any uniform grouping, however little, well scattered over the field. His conclusions are as follows: (1) That the serum of nondysenteric adult patients does agglutinate the Shiga and acid type (Flexner) bacilli frequently in dilution of 1 : 20, and occasionally in a dilution as high as 1 : 100. (2) That this agglutinating power is wanting in the blood of nondysenteric young infants (under one year), rarely being present even in a 1 : 10 dilution. (3) That there are certain differences in agglutinating capability between the Shiga and acid type (Flexner) bacilli, the former, in these tests, clumping more readily than the latter. (4) That a decided and prompt reaction, under two hours, with the Bacillus dysenteriæ in dilutions of 1 : 20 or higher in young subjects (under one year) and 1 : 50 or higher in older persons who have not recently suffered from chronic or subacute intestinal disease is probably pathognomonic of acute epidemic dysentery.

Flexner[79] claims that the serum reactions of cases of dysentery are of the greatest importance, indicating a close relationship between the bacilli from Japan, Manila, Porto Rico, and Germany, and rendering probable the identity of the epidemic dysentery of this country with that of the East and Germany.

S. Ito[80] has isolated a bacillus from a peculiar form of dysentery in Japan, which organism resembles the colon bacillus. The organism was agglutinated by the serum of patients recovering from the disease, while the serum of normal individuals or of those who had suffered with dysentery or acute enterocolitis had no effect. The serum of patients recovering from the disease did not cause clumping of the dysentery, colon, or typhoid group of organisms.

Jürgens[81] in a garrison epidemic of dysentery, comprising 26 cases, isolated from the feces a bacillus resembling that described

by Kruse. It differed, however, from the latter organism in its forming acids on mannite agar, and resembled more closely Flexner's bacillus. It was agglutinated by the serum of the patients in dilution of 1 : 100 up to 1 : 500 and even higher, while no agglutination occurred with the bacillus of Kruse.

Hewlett[82] tested a number of cases of dysentery for the agglutination reaction upon a strain of the Bacillus dysenteriæ obtained from Dr. Flexner. All the cases, with one exception, failed to give the reaction, while two or three cases of other diseases gave the reaction. The case of dysentery which reacted was one of amebic type, though there may have been a double infection. Two fresh cultures of the B. dysenteriæ, a Shiga and a "Flexner" strain, were used, and of 4 cases of dysentery 3 reacted markedly, and the fourth slightly. An amebic case did not react at all. Two cases of asylum dysentery also reacted well. It was noteworthy that these cases reacted with the Flexner strain only and not with the Shiga bacillus.

Hiss and Russell[83] isolated from a case of enterocolitis in a child an organism that presented many points in common with Shiga's bacillus, but was agglutinated by normal horse serum and anti-typhoid serum.

J. H. M. Knox[84] in a series of cases of infantile diarrhea from which a bacillus was isolated resembling the B. dysenteriæ (Shiga) obtained a positive agglutination reaction in 10 out of 13 cases during the first week of the disease. "As the reaction persists in the chronic cases for weeks or months, it is in this class of cases that the blood tests may prove useful."

Cordes[85] examined the stools of 51 patients suffering from gastrointestinal diseases. The B. dysenteriæ was found in 26 cases. In 25 the acid mannite type of the bacillus was found; in 1, the alkaline mannite form. Agglutination as high as 1 : 3000, and 1 : 3500 was obtained with the bacillus of the acid type in 6 cases. The blood of 45 patients was tested with the Harris and Shiga dysentery bacilli in dilutions of 1 : 40, or 1 : 50, with a positive agglutination in 10 cases.

Bergey,[86] in an article on the reaction of certain water bacteria with dysentery-immune serum, concludes that, (1) the agglutination reaction with dysentery-immune serum cannot be relied upon in the differentiation of organisms of bacillus dysenteriæ group un-

less we know the limits of the agglutinating power of the serum employed for the particular organism against which the animal has been immunized. (2) The normal serum of the horse, rabbit, and dog contains agglutinins in relatively small amounts for a variety of organisms. (3) The immunization of an animal against a particular organism increases not only the agglutinins for that organism, but likewise induces an augmentation of the agglutinins of other organisms which are closely related in their receptor apparatus.

Van de Velde[87] was the first to demonstrate agglutination of streptococci by immune sera. He studied the action of the serum of horses which were artificially immunized against streptococci. (Quoted by Weaver.[88])

Bordet[89] observed agglutination reaction occurring between anti-streptococcic serum and cultures of the Streptococcus pyogenes.

Salge[90] found that streptococci isolated from cases of scarlatina were agglutinated by the serum of patients in dilutions up as high as 1 : 500. (Quoted by Weaver.)

Wlassjewski[91] obtained agglutination with streptococci obtained from different sources and an antistreptococcic serum. Serum from a case of puerperal fever agglutinated the Streptococcus pyogenes in dilutions of 1 : 400.

Moser and Pirquet[92] claim that for streptococci the macroscopic test is more readily done, but the reaction is better observed and the details more evident in the microscopic method. Neither shows an advantage in the constancy of the reaction, both evincing great variations. They injected a horse since the first of the year 1900 with streptococci derived from the heart's blood of scarlet fever patients. This serum agglutinated the strain of streptococci injected, microscopically and macroscopically, in dilutions of 1 : 1000. With one exception, it agglutinated streptococci taken directly from the heart's blood and lymphatic abscesses. The streptococci derived from other sources besides scarlet fever did not agglutinate at 1 : 1000, but a streptococcus isolated from an empyema gave the reaction in a dilution of 1 : 250. They conclude that streptococci from the blood of scarlet fever patients, when cultivated upon artificial media for some time, will agglutinate in an immune serum produced by similar streptococci. They find that agglutination of the streptococcus with the serum of scarlet fever

patients occurs in 54 per cent. of cases. The agglutination in scarlatina is more marked in severe than in mild cases.

Perkins and Pay[93] found that some cultures of the Streptococcus pyogenes isolated from the blood and lesions of variolous patients gave a positive agglutination with the antiserum used in the treatment of variola. The method of Meyer was adopted, in which only those cultures which diffusely clouded bouillon were used. Of 9 cultures tested against the antiserum, only 1—and that the one used in the preparation of the serum—was agglutinated by it, while in two other cultures there was a feeble reaction, but not conclusive.

H. de Waele and E. Sugg[94] isolated a streptococcus from the heart's blood in cadavers dead of variola. This organism was agglutinated by the blood of all patients having variola, and conversely the serum agglutinated any of the streptococci isolated from other cases of smallpox, but not other streptococci, except those which were specific for diseases which the patient passed through. The serum of every vaccinated individual also agglutinated this streptococcus, but less so than after an attack of the disease. The serum of nonvaccinated individuals or of newly born infants possessed no agglutinating power.

Piassetzka[95] finds that the antistreptococcic serum of rabbits agglutinates completely homologous streptococci, but that heterologous serum rarely produces a complete reaction and more often no reaction at all.

H. Schiller[96] points out by experiments that serums which have been produced with virulent and unchanged streptococci agglutinate very promptly all the forms of streptococci.

Aronson[97] has produced a highly valent serum which has brought about agglutination with all forms of streptococci derived from pathologic processes, such as angina, erysipelas, sepsis, scarlet fever, and acute articular rheumatism. As a result of numerous experiments, Weaver has found that in streptococci cultivated from cases of scarlatina, some are agglutinated by almost all scarlatinal sera, but at dilutions varying from 1 : 60 to 1 : 400; others are agglutinated by the same sera with less constancy and at lower dilutions, and many are not agglutinated at all. Streptococci cultivated from cases of scarlatina are agglutinated by serum from cases of lobar pneumonia and erysipelas in about the same dilu-

tions as by scarlatinal sera, and in the case of erysipelas at even higher dilutions. The same appears to be true of typhoid serum so far as limited tests indicate, and to almost the same extent of puerperal fever serum. The agglutination reaction between the streptococci cultivated from cases of scarlatina and the serum from cases of scarlet fever is in no way specific, and cannot be of any value as a means of diagnosis. The effects produced by heat and the slight alteration of reaction of the media serve to emphasize the importance of very exact methods in the study of agglutination phenomena in connection with streptococci as well as with bacteria in general.

Plague. Wyssokowitz and Zabolotony[98] state that the agglutinative power of the serum in cases of plague is not manifest during the earliest and most acute stage of the disease. It first appears in the blood about the seventh day of illness, gradually increases until the fourth week, and declines after this period. In cases fatal during the first week of illness they found it absent.

Polverini,[99] in regard to the agglutination reaction in plague, claims that it may not be present in severe cases during the first ten days of the disease, and hence concludes that it is of little value.

In 25 cases of plague Cairns has obtained a positive agglutination reaction in 20 in dilutions of 1 : 10 and 1 : 25. In no case has an undoubted reaction occurred in dilutions higher than 1 : 75; quite a number (10) gave the reaction in dilutions of 1 : 50. The agglutinative phenomenon is most marked after the second week of illness, and the agglutinative power, insignificant at the commencement of the illness, progressively increases up to the sixth or seventh week of the disease. It then declines, but may be present in well-marked cases four or five months after the primary illness.

Raw[100] states that the plague commissioners came to the conclusion that the serum diagnosis of plague was of no practical value, inasmuch as while the observation takes at least twenty hours to give pronounced opinion, the clinical features of the disease develop with such rapidity as to leave no doubt of the nature of the affection.

Paratyphoid. W. P. Johnston[101] reports 4 cases of paratyphoid fever. The serum from 2 of these cases agglutinated the para-

typhoid bacillus isolated from the blood. In the other two cases the diagnosis was made upon the ability of the patient's serum to agglutinate Gwyn's paracolon bacillus and the organism isolated from the other two cases. In all 4 cases the Widal test was negative. This report includes Gwyn's case. Of 194 cases of enteric fever in which the agglutination tests were made with the bacillus "O" and Gwyn's paracolon bacillus, the results, except in the 4 cases mentioned above, were negative.

Hewlett mentions Achard and Bensaude's[102] 2 cases of paratyphoid fever in which the Widal reaction was negative throughout. Agglutination reaction was positive, however, with the bacilli isolated, in one case from the urine, and in the other from pus, in the right sternoclavicular articulation. He then reports a case coming under his observation where the serum of the patient gave a positive reaction (with a bacillus obtained from the blood) in dilution of 1 : 100.

Longcope (quoted by Hewlett) reports a case of paracolon infection in which the serum of the patient gave a reaction in dilution of 1 : 200; with Gwyn's bacillus at 1 : 500; with the Cushing bacillus, 1 : 200; and "Carlez" bacillus, 1 : 30. The serum also agglutinated the typhoid bacillus in low dilution.

The work of Cushing[103] with the bacillus "O" isolated from a costochondral abscess which was agglutinated by the patient's serum in a dilution of 1 : 800, and that of Schottmüller[104] with cases similar to those of Gwyn, are too well known to require elaboration here.

Wells and Scott[105] isolated a bacillus which was agglutinated by the patient's serum in dilutions of from 1 : 40 to 1 : 50,000 in a case of paratyphoid fever. Four Widal reactions were made on different days, and all were negative.

Kurth,[106] in 5 cases of Bremen gastric fever, isolated from the feces of one, and from the urine of another, bacilli which were agglutinated by high dilutions of the serum of 4 of the cases.

Brion and Kayser,[107] Libman,[108] and Hume,[109] have each observed cases and isolated organisms that resemble, yet differ from the typhoid and colon bacilli, which were agglutinated by the serum of the patients.

DeFeyfer and Kayser[110] report an epidemic of paratyphoid fever. Fourteen cases were observed, and the serum of all the cases

agglutinated paratyphoid bacilli of the type "A" and "B" of Schottmüller.

L. F. Jermain[111] reports 3 cases of paratyphoid fever, the duration of the illness being sixteen days. The Widal reaction was negative in each case, though in one serum reaction was positive with Gwyn's paracolon bacillus.

Kayser[112] describes two organisms isolated from cases of paratyphoid, one belonging to the "paratyphoid group A," and the other to "group B." He thinks that all cases thought to be typhoid fever should be tested with three groups of bacteria—the typhoid bacillus and the two groups of paratyphoid organisms. The same writer[113] observed three patients suffering with paratyphoid fever, the diagnosis being made upon the basis of a specific agglutination in high dilutions (1 : 100 and 1 : 1000) with Schottmüller's paratyphoid bacillus (type B).

Bertrand Smith[114] reports 2 cases of paratyphoid infection with positive agglutination reactions in dilution of 1 : 50 up to 1 : 2000, with the serum of the individual and with the serum of immunized animals.

Walker reports a case of paratyphoid fever in which the Widal reaction was negative.

Colon Bacillus. Le Sage,[115] in 40 out of 50 cases of enteritis occurring in infants, isolated the Bacillus coli communis, which was agglutinated by the blood of all the patients.

Johnson and Goodall[116] have experimented to ascertain the effect of the action of blood serum in the different forms of insanity on cultures from mixed strains of the Bacillus coli in order to determine whether by the agglutinins direct evidence could be adduced as to the influence of the colon bacillus in such cases or the indirect evidence of a similar action on the part of other organisms related to the colon bacillus. In all 25 cases were employed. Good agglutination occurred in 4 out of 5 cases of acute melancholia; 1 out of 3 cases of general paralysis; 1 out of 2 cases of delusional insanity. Partial agglutination appeared in 6 out of 11 cases of acute mania; 1 out of 2 cases of delusional insanity; 1 of alcoholic insanity. No agglutination occurred in 5 cases of mania, 1 of melancholia, 1 of puerperal insanity, 2 of general paralysis, 1 of recurrent mania. Agglutination, therefore, was present in 60 per cent. of all cases, in 28 per cent. good and in 30 per cent.

partial. With control experiments, which were made each time, only 1 showed a slight partial agglutination.

Bruce[117] found in the blood in a case of acute mania a short bacillus growing singly, in pairs and chains, which was partially agglutinated by the blood of five other patients suffering from acute mania.

Micrococcus Melitensis. Musser and Sailer[118] obtained a positive agglutination reaction with the bacillus melitensis in a case of Malta fever.

Wright and Smith[119] also obtained the same reaction.

P. W. B. Smith[120] reports a case of Malta fever in an officer, who, after three years, still has irregular attacks, and whose blood reacts with well-marked agglutination in dilution of "1 in 40 and over."

W. B. Banister,[121] in a patient who had been in the Philippines, where he had been suffering from a fever thought to be malarial, found that the disease presented the clinical features of Malta fever. Serum reaction with the Micrococcus melitensis was evidenced by marked agglutination.

In Mediterranean fever Aldridge[122] obtained a positive reaction in 30 of 34 cases with the Micrococcus melitensis.

Miscellaneous. Vagedes[123] states that we can sometimes show in the blood of patients recovering from influenza a body that gives rise to agglutination of the influenza bacillus.

Wildbolz[124] observed agglutinating bodies in the serum of guinea-pigs intraperitoneally inoculated with cultures of the gonococcus grown upon serum bouillon; the animals developed emaciation and other symptoms. He tested old cultures of the gonococcus as well as young cultures, and found the agglutination reaction positive. In two cases of gonorrhea, one of which presented epididymitis and elevation of temperature, no agglutination reaction occurred, while in the second case the serum reacted with a young culture of the gonococcus and not with an old culture. He also found that the serum of normal guinea-pigs and the serum of man did not give this reaction with the organism.

Lerch[125] obtained a positive reaction in one case of yellow fever with the Bacillus icteroides in dilution of 1 : 10 and 1 : 40 upon the second day of illness.

Archinard and Woodson[126] claim to have obtained agglutination

with the bacillus of Sanarelli in 75 per cent. of the cases of yellow fever.

Reed and Carroll[127] have shown that the same reaction occurs with the bacillus of hog cholera in a small percentage of cases of yellow fever.

Pothier,[128] in 154 cases of yellow fever, failed to get a positive agglutination test with the Bacillus typhosus. In 19 cases the serum reaction was tried with the Bacillus icteroides with slow clumping and without loss of motility in 8 cases.

J. B. Tombleson,[129] during two successive attacks of yellow fever, found a bacillus in his own blood that he recognized in 6 other cases of the disease. The serum of a dog immunized against the bacillus produced agglutination with young agar cultures.

Lowenthal[130] diagnosticated relapsing fever during the apyretic interval when parasites were absent from the blood. The specific agglutination was most marked immediately after the paroxysm, and sometimes became appreciable just before the next chill. Where patients overcame the infection, the reaction lasted longer, and if it persisted for seven days in sufficient intensity to cause cessation of motility of the organisms in one hour, no further relapses ever occurred.

Gabritschewsky[131] found that the blood of a patient who had just recovered from relapsing fever would cause an agglutination of spirilla in a specimen of blood kept in the thermostat for thirty minutes to one hour.

Spronck[132] claims that the serum of lepers, in dilutions of 1 : 60 and 1 : 1000, agglutinates fresh living cultures of the bacillus of Hansen.

In diphtheria the serum test does not at the present day figure in the diagnosis of the disease. The bacilli, however, have been agglutinated by antidiphtheritic serum by Delépine,[133] by Nicolas and Charrin,[134] and others.

Schwoner[135] divides the pseudodiphtheria bacilli into two groups. The first group, the Hoffman type of organism, is agglutinated partially with normal serum, and completely with monovalent and polyvalent serum in dilutions of 1 : 10 to 1 : 2000. In the second group, comprising those bacilli resembling the xerosis bacillus, only homologous varieties are agglutinated with homologous serum.

In tetanus, usually negative results have been obtained. However, Sabrazes and Rivière,[136] by using cultures in a vacuum, obtained clumping with the serum of a patient on the eighth day of the disease. Bordet was the first to show that the B. tetani was agglutinated by serum of normal horses.

Achard and Lannelongue[137] have obtained positive agglutination test reactions with the Proteus vulgaris and Proteus mirabilis in animals immunized against the organism.

Rogers[138] found that the Oidium albicans grew feebly in the serum of animals immunized against it, and formed in masses at the bottom of the tube.

Achard and Bensaude[139] obtained a positive agglutination reaction in 10 out of 14 cases of cholera in dilutions of 1 : 10 and 1 : 20.

SUMMARY. In summarizing it will be seen that of 17,280 cases of enteric fever, 16,352 gave positive reactions and 928 did not; positive, 94.6 per cent.

In paratyphoid fever 42 cases have been collated, and in 40 of these, or 95.2 per cent., a positive reaction was obtained.

In tuberculosis 221 cases were enumerated, and of them 194, or 87.7 per cent., have a positive reaction.

Of 390 cases of bacillary dysentery, 313, or 80.2 per cent., responded to the agglutination test.

In the other diseases only a small number have been reported, and hence no reasonable estimate can be given of the percentage of reactions obtainable.

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February 11, 1904.

Sarcoma of the Bladder and Prostate Gland Causing a Cyst of the Urachus and Bilateral Hydronephrosis in a Nine-months-old Baby.

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In hastily going over some of the literature on the subject of cysts of the urachus one is struck by the great diversity of opinion regarding their frequency and their importance. The great hinderance to satisfactorily determining the origin of many of the extraperitoneal cysts is the impossibility of carrying out thorough histologic investigations. According to the experience of Wutz and of Doran true cysts of the urachus are lined by stratified epithelium, and are contained within a capsule made up of non-striated muscle. These structures, however, may be so modified by long-continued pressure or by inflammation that they can no longer be recognized. Consequently in those cases of large cysts occurring late in life there is always great doubt as to their true origin, the opinion of many investigators being that most of the so-called allantoic cysts are really encysted dropsies due to chronic peritonitis, usually tuberculous. In young children these difficulties as a rule do not arise, but the literature concerning such cases is very scanty, two cases only resulting from my searches.

Before describing the case to be presented I wish to briefly review the formation of the urachus. About the end of the third week of fetal life a small sac develops as a pouching out of the

ventral wall of the gut-tract near its caudal end. This sac protrudes from the still widely open abdominal cavity, enters the extra-embryonic part of the body cavity, and reaches the inner surface of the false amnion, with which structure it intimately unites to form the true chorion. As the walls of the abdomen gradually close, leaving only the umbilical aperture, it is through this opening that the allantois protrudes. The allantois has for its functions the carrying on of the nutrition and the respiration of the fetus until the true placenta is formed, the vessels of the umbilical cord being the original allantoic blood channels. Within the abdominal cavity is that portion of the allantois known as the urachus. It extends as a tube from the umbilicus downward to the hind-gut. At first this gut is of the same size throughout, but gradually certain changes take place. That portion nearest the hind-gut begins to expand to form the urinary bladder, while the distal part undergoes contraction and normally obliteration. At this same time the hind-gut seems to move more posteriorly, and the urogenital sinus appears in between. Eventually there is a complete separation, the anterior tube becoming the bladder, while the posterior becomes the rectum. As the urachus dilates, the tubes from the Wolffian bodies, the future ureters, move forward and are finally situated at the neck of the bladder.

From this description it can be seen how certain malformations may be brought about. If, for instance, the urachus, instead of completely obliterating, remains patulous, a urinary fistula opening at the umbilicus will result. If, however, the umbilical end closes the rest of the tube may undergo a dilatation, and a larger or smaller cavity form, one communicating with the bladder and more or less filled with urine. If the opening between the cavity and the bladder is large and free the persistent urachus would distend and collapse according to the amount of urine present. If, on the other hand, the opening were small and guarded by a fold of mucous membrane, as described by Wutz, the cavity could fill, but might not be able to empty itself. There might also be obliteration at both ends and a cyst in between. Instead of having a single large cavity there may be numerous small dilatations. Wutz on examining the bodies of 74 adults, 38 males and 36 females, found that in 24 of the cases there were enlargements

varying in size from some almost microscopic to others the size of a bean. Of these 24, 15 were in men.

Tillmanns in his *Surgery* mentions 14 cases tabulated by Stadfeldt, of which 12 were in men, the experience generally being that such a condition is more common in men than in women.

These cysts are found in the mid-line of the abdomen, lying between the umbilicus and the top of the bladder, their situation in regard to the surrounding tissues depending as to which portion of the urachus has dilated. They may be completely within the abdominal wall, and be recognized as a more or less well-defined mass. They may, however, occupy a large portion of the pelvic cavity, and be mistaken for various forms of cysts.

Stanley reports an old case concerning which the history is very vague, but which on account of its direct bearing upon the one shown this evening should be mentioned. He reports the case of a boy of two years in whose abdominal wall an abscess was found in the midline and just above the pubes. This was opened and pus and urine escaped. Investigation showed that there was a small opening communicating with the bladder. Apparently it was in this same case that a sarcoma of the bladder was found, and one that in all probability caused an obstruction, the consequence of which was a reopening of the urachus.

Morgan reports a case of a five-year-old boy who was operated upon for suspected peritonitis. The abdomen was entered and a cyst communicating with the bladder and filled with urine was opened. The operator "was certain that the cyst was in the midline, running up to the umbilicus and communicating with the bladder."

The following is the history of the case presented this evening. It is not as extensive clinically as could be wished, as parents were Italian. For that which I have I am indebted to Dr. Woods, of the Philadelphia Hospital.

Victoria La Civita, aged nine months, male. A small mass in the abdomen apparently in the neighborhood of the appendix was discovered, and on account of the child's critical condition it was decided to operate.

This tumor, about the size of a baby's fist, was thought possibly to be an abscess the result of some appendiceal trouble and was

opened. From it there escaped a thin slightly blood stained fluid, at first clear, but finally cloudy. This did not have a uriniferous odor. The patient died within a day following the operation after some temporary improvement.

Autopsy. The abdomen was greatly distended, and at a point midway between the umbilicus and the pubes and a little to the right of the mid-line there was an incision about an inch long in which was a piece of gauze packing. The cavity that had been filled with packing was irregular in shape, and to a slight extent seemed to have penetrated the surrounding tissues. This appearance was seemingly the result of the operative procedures. On removing the gauze a small opening communicating with the bladder was found. The abdomen was opened and the intestines other than being much distended were apparently normal.

The kidneys and ureters showed marked changes, both sides being equally involved. The organs seemed rather larger than usual and were cloudy in appearance. On opening they were both found to contain quite a large amount of cloudy fluid that escaped also from the dilated pelves. The cortex was swollen and cloudy, and the pyramids much injected. Both ureters were much dilated and also very tortuous. With a little difficulty a probe was passed through each ureter into the bladder. This latter organ proved particularly interesting. There was very little change in size, but the walls were much thickened, and the mucous membrane was deeply congested. In some places there was a deposit of pseudomembrane.

The conditions so far found led one to look for some interference to the outflow of urine from the bladder. An examination of the penis showed some phimosis, but nothing marked. An attempt was made to pass a small probe through the external urethra, but it was not successful.

On examining the internal surface of the bladder at the internal opening of the urethra there was found a soft, irregular, light yellowish mass about an inch long and half an inch wide. This was raised somewhat from the surrounding tissues, and was comparatively well defined from the mucous membrane of the bladder. The site of the prostate was examined, and corresponding to its lobes there were found three distinct masses about the size of

filberts; they were almost white in color, and on sectioning narrow glistening bands of fibers could be seen. Portions of the middle lobe of the prostate and of the bladder tumor were removed and prepared for histologic examination. There was also a left-sided inguino-scrotal hernia.

Microscopic Examination. Myxosarcoma.

The characteristics of the two growths are similar except that in that from the prostate there are numerous glandular spaces in one portion of the specimen. The tissue is composed of many cells with round or irregular oval nuclei separated from each other by clear transparent areas in which are numerous fine fibrillæ. The density of the tissue varies greatly in different parts. In some areas the cells are quite closely arranged, while in other portions the intercellular substance predominates. This latter is particularly the case in the neighborhood of the bloodvessels, the walls of which are composed of a very incomplete endothelial lining. There are also many polymorphonuclear eosinophiles scattered throughout the specimen.

On account of the numerous complications the case seemed one particularly interesting for demonstration. It would seem that the new growths in the bladder and in the prostate gland might be considered as the primary cause of the various conditions present.

As has already been shown by the investigators mentioned, Wutz and Doran, more or less incomplete closure of the urachus is by no means uncommon. Taking that as a starting point, it can be readily understood how an obstruction to the outflow of urine would cause a distention of the bladder, and secondarily bring about a dilatation of the incompletely obliterated urachus, thus giving rise to a cystic condition. As the opening found at the post-mortem was quite small, the mucous membrane acting as a valve, as mentioned by Wutz, would tend to retain the contents. The ureters would also become larger than normal, and on account of the stretching would be tortuous. Finally the pelves of the kidneys would dilate and hydronephrosis result.

The inguinal hernia in all probability resulted from the straining of the child when attempting to pass urine.

If the infant had survived the operation a urinary fistula would

undoubtedly have resulted, and, although the hydronephrotic condition would have been relieved, death would have eventually followed from the extension of the malignant tumor.

Discussion.

Dr. Coplin spoke of the diagnostic value of relaxation of the abdominal wall in cyst of the urachus.

March 24, 1904.

A Case of Spontaneous Arrest of Growth in an Endothelioma, with Subsequent Inflammatory Absorption.

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(From the Laboratories of the Polyclinic Hospital.)

M. S., aged forty-three years, Hebrew, has always been healthy; four living healthy children, lost one in infancy; last child twelve years old. Symptoms pointing to beginning menopause are present.

Three years ago there appeared on the posterior aspect of the left forearm, about the junction of the upper and middle thirds, a small nodule beneath the skin, which was movable and painless. In the beginning the patient squeezed and otherwise handled it, on one occasion bringing a little blood. The mass grew steadily and painlessly for six months, in that time attaining its present size. From that time till two weeks before operation it remained stationary. Two weeks before applying for relief the mass began to be painful and to show signs of inflammatory reaction. The mass was excised by Dr. Steinbach ten weeks ago. Two weeks later the wound had healed by primary union. There is no evidence of recurrence. The patient complains of pains through the forearm.

Pathologic Report. The mass is flattened, dense, has a smooth glistening base, as if shelled off from periosteum. On upper surface is a portion of skin, but this is not adherent nor in any way connected with the growth. The mass is flattened, slightly ellip-

tical, 1½ x 2 x ¾ in. It has no capsule, but has an envelope which is derived from the surrounding connective tissue. On section it presents a grayish white appearance composed of dry friable fibrous material.

Specimen fixed and hardened in Orth's fluid; sections cut with freezing microtome and stained with hematoxylin, hematoxylin and eosin, Van Gieson's stain, Unna's polychrome methylene blue, Gram's stain, and Mallory's connective-tissue stain. The following appearances are found: The growth is surrounded with a thin connective-tissue envelope which is continuous with a connective-tissue stroma ramifying freely through the growth. This stroma is arranged so as to form alveoli of large size. These alveoli are filled with what appears under low power and high illumination to be a homogeneous degenerated substance, but which, under close examination, is seen to be made up of cells, closely packed together, sometimes flattened so as to present a stratified appearance. These cell masses are clearly necrotic, as they do not take up nuclear stain, but are stained by eosin in the hematoxylin-eosin process and by picric acid in the Van Gieson's method. Areas are observed where the necrotic process has not taken place. Here we see the alveolus is filled with medium-sized round cells, with round nuclei, staining with moderate intensity. There can be no connective-tissue fibres demonstrated between the cells, and the cell growth is evidently derived from the endothelium of the lymph spaces. That the above cellular necrosis affects such collections of cells as those just described is shown by the fact that the stages of transition from one to the other can be demonstrated. The connective-tissue stroma shows a very peculiar phenomenon. There is active hyperplasia, with a very marked round-celled infiltration. New-formed bloodvessels are numerous. Very characteristic is the development of *giant cells*, which are very numerous and are uniformly applied to the margins of the necrotic cell areas, sometimes completely surrounding an alveolar space like a skirmish line.

Their peripheral arrangements, combined with the fact that they are so closely applied to the cell masses, and often adjust their shape to these masses (being long, slender and flattened), make one believe that their function is phagocytic.

Taking the evidence of the clinical and pathologic reports we are led to the following conclusions:

That a sarcomatous growth started in the subcutaneous connective tissue; that it grew steadily for six months, and then, for some unknown reason, became arrested; that a necrosis or atrophy of the cells of the tumor took place; that later this inactive tissue began to act as an irritant, and the response was a productive inflammatory process which endeavored to remove a foreign mass. The very abundant presence and peculiar arrangement of the giant cells seems to show that the function of these cells is an absorptive one.

Discussion.

Dr. Stengel said that he had under observation a patient with multiple sarcoma in whom the tumor at times disappeared. It was, he said, difficult to understand the disappearance of carcinoma, sarcoma, and tuberculous growths. He had seen tuberculous glandular tumors disappear in several cases. In a case operated upon by Dr. Keen the stomach was found to be studded with nodules, supposed to be carcinomata. The patient apparently recovered and gained in weight. Later a second operation became necessary, and then the stomach showed no growth whatever. The nodules might have been lymphangiectases. In a case of acute leukemia in which the entire body had been covered with whitish nodules supposed to be leukemic in nature, none were visible at autopsy. All the tumors having disappeared, Dr. Stengel was of the opinion that they were lymphangiectasias.

Dr. Randolph, in closing, said that the inflammation present was probably a secondary process, the tumor having been destroyed by necrosis and not by inflammation, the latter being stimulated by the necrotic tissue acting as a foreign body.

April, 14, 1904.

Proceedings

of the

Pathological Society of Philadelphia.

MAY, 1904. NEW SERIES, VOL. VII., NO. 5.

TABLE OF CONTENTS.

COPLIN, The Early Lesions of Arteriosclerosis, with Special Reference to Alterations in the Elastica.—SPILLER, The Earlier Changes in Arteriosclerosis of the Nervous System.—LONGCOPE, The Early Changes in Arteriosclerosis of the Gastrointestinal Tract.

The Early Lesions of Arteriosclerosis, with Special Reference to Alterations in the Elastica.*

W. M. L. COPLIN, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

The cardiovascular phenomena of arterial sclerosis, of which you ask me to consider the early stages, appear to offer the clinician a picture possessing more definiteness and much sharper outlines or delimitations than the pathologist can well appreciate. The very extensiveness of vascular disease is to the clinician the basis of an essential syndrome, for such I take it to be, containing many and varied lesions. The frequency with which certain changes in the vessels and in the heart, and, I might say, the nerves and possibly other superficial soft tissues as well as the viscera, are associated, leads the clinician to infer that this is all part of a general process. With this view I am not at all prepared to take issue; but pathologists are prone to see some major essential feature which constitutes the basis of even a general condition, and make this change the center about which subsidiary alterations can be more or less definitely grouped.

As an example of this method of classifying, or, possibly I had better say, correlating phenomena, let me digress for a moment to call your attention to what, of course, is well known, and, there-

* Read by invitation.

fore, better illustrates the point that I am attempting to make. In those lesions associated with inefficient progression at the mitral orifice—whether due to stenosis or regurgitation—we recognize a tendency toward distention of the pulmonary capillaries, fibrosis and pigmentation of the lung, hypertension of the pulmonary artery, alterations in the right ventricle, including the myocardium, valves, and orifices, eventually marked venous distention, red atrophy of the liver, cyanotic kidney, and an impressive list of concomitant but intimately associated structural alterations manifested by, in some instances, characteristic functional disturbances. Here the pathologist, in common with the clinician, recognizes that the essential feature of these long and rather complicated association of processes—many of them dissimilar—can be traced to faulty execution of function primarily restricted to the mitral area. It may be easy to cite other instances in which widespread alterations depend upon some primary, possibly it would be well to say essential, lesion to which other associated abnormalities are subsidiary or, at least, secondary. Now to apply this somewhat rambling statement to the matter immediately at hand—is it possible for us to recognize in the widespread devastation of advanced arterial sclerosis some primary, and, therefore, necessarily constant, alteration upon which, or rather to which, all other changes are superadded?

Those who are to discuss with us to-night the changes occurring in the alimentary canal, in the central nervous system, and elsewhere, would probably agree that the primary structural alteration lies somewhere in the cardiovascular system. Apparently alterations in this part of the almost universally diseased organism are necessary to the clinical as well as the pathologic concept of the disease under consideration. I think it may safely be predicted that we can look upon the changes in the heart muscle as depending upon alterations in the coronaries or changes in stress, or both, and, therefore, that the early lesions of arteriosclerosis are not to be sought in any primary change occurring in the myocardium. Such changes may be correlated, and possibly some alterations may precede important structural modifications in the cardiac blood supply ; but still, I take it, the essential alteration must be sought in the arteries themselves. Here we are at

once confronted by difficulty in determining exactly what is the constant or more nearly constant change in the vessels. Pathologists see mainly evidence of structural change in the artery, arteriole, capillary, and vein, justifying the terms angiosclerosis used by Thoma,[1] and vasculitis, with essentially the same meaning adopted by Weichselbaum.[2]

Before going farther let me suggest that the term sclerosis has its limitation, as Gibson[3] properly suggests; even Thoma, who is rather an extremist, would not take the ground that the whole of the vascular change is covered by the term sclerosis. Sclerosis, in the sense that the vessels are harder, that there is an actually induced induration as an essential part of the process, is true only in part. Vessels may be, in certain stages of the change under consideration, without conspicuous fibrosis or other alteration such as one would ordinarily consider an important feature of the general picture of so-called arteriosclerosis. Coats and Auld[4] further urge objections to the term sclerosis, as it implies hardening, while ignoring the new formation of tissue that they consider is the fundamental factor in the process. Mott, in a way, evades and possibly improves this concept by the use of the term degeneration, speaking of cardiovascular degeneration or arterial degeneration, but here the idea of degeneration as it appeals to the pathologist seems to be somewhat different from the picture confronting the clinician. Both are right, but each looks at the shield from a different point of view. The clinician sees degeneration and retrograde change, manifested probably by functional inefficiency or inadequacy. The pathologist looks for some structural lesion that falls within a definite catalog or class, the limitations of which are often arbitrary, sometimes illogical, and they may be impossible to determine with any degree of accuracy.

As a further complication to a clear appreciation of the morbid process under consideration we are embarrassed by the multitude of alterations, the relation of which, one to another, in the present state of our knowledge, cannot fully be appreciated. Before the appearance of Rokitansky's book (1846) the different stages of atheroma were only confusedly recognized, and not until 1856[5] did this eminent worker and thinker fully crystallize and unify previously conflicting and discordant views. The morbid anatomist

wishes more specific information upon the position, in our scheme, of easily recognized lesions, aneurysm, ectasial arteritis, the obliterative arteritis of Friedländer,[6] endarteritis proliferans, the thrombosing arteritis of Thoma, the angiosclerosis preferred by Thoma to arteriosclerosis, arteriolitis used by Letulle[7] and others, the peri- or endarteritis of syphilis or that type of endarteritis luetica (Heubner), or the hereditary syphilitic arteritis of Barlow;[8] the periarteritis of Kussmaul and Maier,[9] and the superarterial subepicardial fibroid nodular lesion described by Knox; the so-called spontaneous endarteritis that Camuset[10] thinks is a manifestation of arteriosclerosis, the endarteritis cartilaginosa of Marburg, senile calcification of the arteries, held by Coats and Auld not to be atheromatous, the arterial hypermyotrophy of Savill, the specific degenerative cortical arterial lesions discussed by Berkeley.[11] Where and how we shall correlate all of these or how many of them enter into the clinical picture of arteriosclerosis, it is impossible at present to say.

Two of the most conspicuous and most constant arterial changes in the condition under consideration are atheroma and the arteriocapillary lesion called by Gull and Sutton[12] a fibrosis, but recognized by a number of other writers as being but part of a change involving arterioles, and called by some writers arteriolitis. Even here authorities are not uniform, Ziegler and Thoma among the pathologists, and most German clinicians make atheroma and arteriocapillary fibrosis parts of arteriosclerosis. The French just as persistently adhere to the belief that the arteriole change is distinct from that lesion involving large trunks or relatively large branches, and called by various names, among which the most popular are atheroma, nodular arteritis and arteritis deformans, as used by Virchow. Letulle[13] says chronic arteritis affecting the aorta is atheroma, involving the arterioles it is arteriosclerosis, but we voluntarily confound the two conditions.

The ablest English writers are divided upon the question. Mott apparently includes almost everything under the head of arterial degeneration, making this practically synonymous with arteriosclerosis as used by the German writers. Russell[14] just as consistently, and I think with great force and propriety, insists that atheroma is a distinct form, though it may be coincident with

changes involving the arterioles. For the purpose of this discussion the change in the capillaries associated with arteriosclerotic edema and important nutritional disturbances may be excluded, and whatever early changes I may discuss with you can be grouped under the head of arteritis, with the distinct reservation that the inflammatory character of the process is by no means established. It is not necessary to retrace all the views suggesting the inflammatory nature of the affection, although no less an authority than Virchow[15] saw in atheroma changes that he regarded as manifestations of inflammation. The important change, and it seems to me the primary alteration upon which we should focus our inquiry, is the change in the smaller arterial branches, and it is to a study of this change that I would particularly invite your attention. Without at all committing ourselves as to its inflammatory nature, which I am rather inclined to disregard, it may be well for us to look for a moment to the causes, or at least such etiologic factors as appear to be in more or less intimate relation with the change in question.

Certain of these causes may be extrinsic or exogenous, arising from without. Among these causes will be classed alcoholism, plumbism, possibly the noxious influences of tobacco, and other preformed poisons, a list of which need not be given. Of the poisons arising within the body should be mentioned those active in intestinal intoxication, which may have something to do with the evolution of arterial disease; the exact nature of the active toxic product is unknown. Whether it is some absorbed bacterial toxin, some normal excretory product of the intestine, some result of proteolytic changes going on in the alimentary canal, some normal or abnormal secretion, remains yet to be determined. The French school strongly urge the influence of alimentary intoxications in the production of arteriosclerosis, and Bergouignan[16] thinks the benefit of a milk diet rests largely upon (1) the admitted diuretic action of the milk, and (2) its very low toxicity. The view of Huchard and also Runeberg, that endarterial disease is due to a toxin in the blood, while possible, remains unproven. Von Noorden found arteriosclerosis in 155 of 343 diabetics, and Feiner noted the frequent association of the two conditions; Grabe[17] thinks that possibly some cases of diabetes can be attrib-

uted to sclerosis of the vessels in the floor of the fourth ventricle. Gilbert and Lion[18] claim priority[19] in the demonstration that atheroma could be induced by the injection of bacterial toxins. If injection of toxic bodies of a kind normally produced within the intestine can be responsible for arterial lesions, then we should expect to find in the blood of arteriosclerotic patients agglutinating reactions against certain of the intestinal flora. While this problem has been studied it is not yet definitely established that certain members of the intestinal flora yield toxins whose action determines the occurrence of arterial disease. Therese[20] has shown that the toxins of bacteria can cause acute arteritis; streptococcus filtrates produce the same vessel changes as unfiltered cultures. Gilbert and Lion[21] state that arterial lesions may be produced through bacterial action in one of three ways: (1) combined trauma of the vessel and infection, (2) cultures of microbes, (3) toxins.

Undoubtedly an important factor in the production of arteriosclerosis is overwork; this excessive demand thrown upon the circulatory organs may be a response to active brain work, such as occurs in professional men, men of affairs, gamblers, and speculators. Hill and Oliver have shown instrumentally that cerebral activity raises the blood pressure. Excessive vascular demand seems to have much to do with the production of the disease in question. This is shown by the at times almost local occurrence of arterial change; for example, in the arms of blacksmiths, and in all the limbs of overworked horses. Our president[22] lays particular stress upon overeating as a cause. This may mean overwork on the part of the digestive and absorptive apparatus, or it may indicate the introduction of foods containing bodies rich in toxic qualities or possessing a molecular constitution rendering them easily converted into toxic products.

Some of the internal secretions, about which we know so little and speculate so much, undoubtedly possess the capacity to produce important circulatory disturbances. Clinically, these are recognized when thyroid products in excess enter the circulation and in the highly selective therapeutic action of adrenal origin. Josue[23] has produced atheroma by the repeated intravenous injection of adrenalin in rabbits, using 3 drops of a 1 : 1000 solution, given on alternate days, the lesion usually appearing after 5 or 6

injections. His results have been corroborated by Gouget.[24] The last-named observer suggests that possibly arteriosclerosis in all its forms depends either upon direct or indirect action manifested through the adrenal. In a guinea-pig which had received during one month a daily dose of 50 cgm. of carbonate of lead there was found at autopsy marked arteriosclerosis and adrenals nearly double the normal size. Sargent[25] has shown that there is an infectious suprarenalitis which may give rise to sudden death in an infectious disease, for example, pneumonia. Harbinson[26] reports a case of a woman, aged forty-seven years, with bronzing of the skin, showing a distribution characteristic of Addison's disease, and in which also the indications point to arteriole change, as shown by the presence of symptoms of Raynaud's disease, affecting the hands, nose, and ears. Vaquez[27] reports a case of persistently high arterial tension, which at autopsy showed an adenoma of the adrenal. The same observer suggests that in saturnism there may be an adrenal irritation that is responsible for the change in tension and the tendency to arteriosclerosis. In the discussion Josue referred to his experimental studies, and stated that, with Bernard, he was at present studying the adrenals from cases of atheroma; they have reached the conclusion that in such cases the glands show evidences of increased activity. These scanty observations with regard to the relation between adrenal activity and arteriosclerosis are highly suggestive and demand careful clinic and experimental study and further observation.

In 1901 one of the assistants in the laboratories of the Jefferson Medical College Hospital expressed a desire to study the normal histology and diseases of the adrenals, and for this purpose we collected a large number of these organs. From pressure of other duties the study remains uncompleted. I have gone over sections from some of these and find 22 cases of arteriosclerosis in which sections from one or both adrenals have been prepared. Only five of these are not markedly altered, and in 4 of the practically normal specimens but one of the pair has been available for study. The change does not seem constant, and the amount of material is inadequate for sweeping conclusions; in 8 there are areas of necrosis, in 5 marked increase in the fibrous tissue, in 3 tuberculosis, and in 1 a secondary neoplasm. In but two instances

(sclerosis 1, tuberculosis 1) is the disease bilateral, and in neither of these is it of the same degree in both organs. In one case I have been unable to detect any lesion that could be presumed to have a specific value, although, in common with other sections, the cells of the medulla are granular, often shrunken from the surrounding reticulum, and but feebly tingible by the usual dyes. As most stain-reactions are essentially chemic phenomena, variation must be looked upon as resulting from some alteration in the chemistry of the affected elements. In the light of Josue's experiments this phase of adrenal action merits most careful inquiry.

There seems little doubt nowadays that the change recognized as an acute arteritis occurring in typhoid, scarlet fever, variola, influenza, and other infectious diseases of an acute nature, may constitute the basis upon which the more general arteriosclerosis can be implanted, often not becoming evident until months or possibly years after the infectious process to which it was due has passed away. Bureau[28] has described the clinical features of acute inflammation of the aorta. Ford[29] has collected 18 cases of acute arteritis in influenza. Letulle[30] thinks the acute arteritis is often preliminary to chronic arteritis, atheroma, arteriosclerosis and aneurysm. Holst[31] reports an acute aortitis secondary to gonorrhea and arthritis, and terminating in aneurysm; there was cellular infiltration extending through the media and adventitia, and containing cocci. A similar case is reported by Moore.[32] Rabe[33] and other observers state that acute aortitis and proliferating endarteritis may accompany acute rheumatism; the coronaries, and hence the nutrition of the heart, may be affected. He places acute rheumatism among the causes of arteriosclerosis. Hess[34] reports two instances of thrombophlebitis complicating acute rheumatism.

Mallory[35] described proliferative changes in the endothelium of the vessels in typhoid, and while he made no suggestion that it might constitute an initial stage of inflammation of these structures, one can easily understand the possibility of such being the case. Thayer,[36] in his articles discussing arteritis and arterial thrombosis in typhoid, has fully considered the arterial lesions that may accompany enteric fever, and the subject is reviewed by Steiner,[37] who reports a most instructive case. The reasonable assumption with regard to the thromboses seen in typhoid is that they must

depend upon some endovascular lesion; Rolleston[38] thinks they are usually bacterial, and Wright[39] suggests that the excess of lime salts resulting from a milk diet may be contributory; still the conviction that thrombosis means, in most instances, inflammation involving the intima of the vessels affected, may be taken as established, and, therefore, constitutes an argument in favor of the belief that typhoid often is attended by endovascular alteration, which may form the basis of later degenerative change. That other infectious diseases, to varying degrees, attack the integrity of the vascular wall is further supported by the studies of Orlowski,[40] who collected 36 reported instances of thrombosis of the abdominal aorta in infectious diseases; Oettinger[41] describes localized ateriosclerosis occurring in the young, and due to, or at least following, acute infective disease. Simitzky[42] has shown that arteriosclerosis has no specific age limitation, and, when occurring in youth, there is a responsible basis for the assumption that the acute infectious diseases may indirectly lay a foundation for subsequent sclerotic changes.

The relation of renal disease to arteriosclerosis is too well known to demand any special mention. Syphilis as a factor is admitted, but we are unprepared to adopt the view of Williams,[43] who holds that syphilis is the chief cause of arteriosclerosis as well as aneurysm. Whether the arterial changes associated with gout and lithemia depend upon these conditions or upon the causes that give rise to them is not established.

Clinicians are prone to lay great stress upon age as an etiologic factor in the production of arterial disease, but the condition is by no means restricted to the aged. Jacobi[44] collected 28 cases, and reported 1 of aneurysm in early life. Fenomenoff has reported a congenital aneurysm of the aorta. LeBoutillier[45] has collected 33 cases of aneurysm in persons under twenty years of age. Black[46] reports a popliteal aneurysm in a boy of ten years. Andral has observed calcifying aortitis in a girl of five years. Moutard-Martin records an instance of atheroma in the arch of the aorta in a boy about two years of age. Berghinz[47] reports an autopsy on an infant eighteen months old with arteriosclerotic changes in the heart; typic lesions of syphilis were also present. He refers to another similar case. Adler[48] states that Young observed sclerotic arterial changes

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in an infant of fifteen months, Meigs in an infant of five months, and Seitz found, in 148 cases of arteriosclerosis, 17 patients who were between ten and twenty-nine years of age. In the discussion of Adler's paper Brill[49] referred to a well-marked case in a girl of twelve years, verified by autopsy; Brill and Libman[50] also review arteriosclerosis in early life. Riesman[51] reports universal calcification of the arteries in a boy of three years. Hirtz[52] has seen probably a dozen cases in children. Filatoff[53] and Barlow[54] have described arteritis in the young. Erichsen[55] has observed atheromatous patches in children three, five, and seven years old. Simitzky's observations are referred to above. The writer[56] has seen instances in childhood, and has recorded a case in which congenital dislocation of the hip in a child dying at the age of seven was complicated by evident arteriosclerosis. M. Crorie submits data which, in my mind, adequately demonstrate that we have laid too much stress on age, sex, alcohol, and syphilis as causes of atheroma. Many observers have shown that individuals may be very old and show no arterial degeneration. The most advanced age of which I can find any record is the often-quoted case of Thomas Parr, who died at the age of one hundred and fifty-two, and whose arteries were described by Harvey as showing no evidence of degeneration. Broadbent says that in long-lived families arterial tension is low. It is a clinically observed fact that those who live to an advanced age commonly possess arteries relatively free from sclerotic change.

Osler suggests the occurrence of tissue inadequacy as a cause of arteriosclerosis. Bruce,[57] under the term "family heart," refers to people whose cardiovascular system is affected by the stress of less than fifty years, and often fails early, sometimes before thirty; three to five or more members of the same family may be affected. In some instances of arteriosclerosis heredity seems implicated; Herrick[58] mentions a family of this kind, and such cases may resemble those falling within the term "family heart" used by Bruce. Adler[59] thinks hereditary predisposition an important factor. Whether the condition inherited be heightened tension, tissue inadequacy, in Osler's sense, or a proclivity to the excessive production of or abnormal sensitiveness to certain poisons is not known.

Von Manteuffel[60] has observed, in limbs amputated for frost-bite, the evidences of arteriosclerosis, and has produced the initial lesions of the disease by spraying the legs of rabbits with ether. He thinks the late appearance of gangrene after freezing is due to the slowness with which obliterative lesions develop in the affected vessels.

Allbutt[61] suggests that, omitting obliterative arteritis, neuritic arteritis, and periarteritis nodosa, the following classes of arteriosclerosis may be suggested: (1) The involuntary—common to old people, often hereditary, not necessarily or usually associated with rise of arterial pressure; the nature of this form, whether intrinsic or extrinsic, does not lie in high living. This kind, he states, may be vaguely referred to as the "faltering rheums of age." (2) The mechanic—the result of long-persisting high blood pressure of whatsoever origin. (3) The toxic—due to such causes as lead, alcohol, or syphilis, usually met with in younger persons, in some of whom pressure rises, in others not.

The foregoing does not by any means cover the causes or conditions with which arteriosclerosis may be associated, but, with all these varied factors, what seems to be almost, if not quite, the constant feature of them all? At some time or another in the evolution of each there is a marked rise in arterial tension. Gowers,[62] Moxon,[63] Allbutt, and a number of equally discerning observers accept vascular stress, at least in part, as an influential factor in the production of atheroma. Williams, in discussing Broadbent's paper, thinks that the high arterial tension of arteriosclerosis in the earlier stages at least is due to an effort at excretion of a poison. All writers on disease of the cardiovascular system lay particular stress upon this heightened blood pressure; by some it is called by a name indicating exactly what it is—heightened arterial tension. Others have given it a special name. Clifford Allbutt[64] terms it his "own jade" hyperpiesis. Russell calls it arterial hypertonus.[65] Savill[66] includes the change under the head arterial hypermyotrophy.[67] McCrorie[68] thinks mechanic irritation is not the exciting but the chief predisposing cause of atheroma. He thinks it depends on an irritant acting on the fenestrated membrane of Henle, by way of the vasa vasorum, but the nature of the irritant is unknown. According to McCrorie,

atheroma always begins in the membrane of Henle, adjacent to the media.

Sherrington[69] believes that the main work of the heart is expended, not directly in propelling the blood, but in dilating the arteries. This work must be increased as a result of high tension, from no matter what cause, and again increased blood pressure must throw extra strain upon the vessels throughout their course. The recognition of this fact has led to inquiry as to whether this recurring exercise of the muscles presiding over the arteriole can produce hypertrophy of the muscle elements in the wall of the vessels.

Russell[70] thinks recurring or persisting hypertonus is, under suitable conditions, associated with an increase in the muscle layer. Grassmann[71] thinks that arteriosclerosis is, in a way, a diffuse neoformation in the vessels, with a certain tendency to malignancy; he believes that the process is initially hypertrophic, although later associated with inflammation and degeneration. Gibson[72] pictures thickened media as an evidence of increased quantity of unstriped muscle in that structure. The usual methods resorted to for determining the relative thickness of the media by comparing it to the total thickness of the wall of the vessel, or to the diameter of the lumen, or estimating the relation between these factors, cannot be trustworthy, as no one can estimate how much contraction has occurred postmortem, and, therefore, to what degree the thickness of the muscle wall and transverse diameter of the vessel have been influenced. Herringham[73] has attempted to overcome the technic difficulties besetting such inquiry by counting the muscle nuclei on longitudinal and transverse section, recognizing that no matter whether the vessel be distended or contracted, the number of nuclei should remain the same in the absence of hypertrophy. He could recognize no increase in the muscle coat, and while his method constitutes a distinct advance, it is open to objections similar to those already mentioned. Savill[74] described thickening of the middle layer, which he called arterial hypermyotrophy. While there is a general agreement that the demonstration of hypertrophy in the media is beset with difficulties that cannot at present be overcome, there is equally a unanimity of opinion that sooner or later degenerative changes occur in the media, and between that

membrane and the intima, often influencing the latter, and marked by hyaline and fibroid transformation, to which reference will be made later.

The views of Thoma[75] have been extensively promulgated and very generally accepted. With his students this eminent authority has collected data to establish the correctness of his opinion that the initial change in arteriosclerosis, following the increased tension, is a widening of the arterioles, followed by reduction in the speed of flow, which in turn gives rise to proliferative changes in the intima of the widened artery, bringing about a readjustment of the vascular lumen. I gather from the writings of Thoma and his students that the relaxation of the vessel wall is to be regarded as depending upon what might be termed muscle fatigue incident to the maintenance of continuous tension. While constantly referring to the loss of elasticity in such vessels primarily, he laid no particular stress upon alterations in the elastica, to which I am convinced we should look for some, if not all, of the initial alterations upon which the change in question must depend. If, as is held by Thoma, the proliferation of the intima is in response to a lessened pressure, then we should expect it to be uniform and not excentric, as commonly observed. The same response might at this moment be inserted with regard to the belief that the proliferative changes in the intima depend upon the presence of an intravascular irritant. As is well known, vessels showing the earliest stages of the sclerosis commonly manifest it only in a part of the wall. Asymmetry in distribution is one of the most constant features of the changes, both early and late, and the signet-ring appearance of sectioned sclerotic vessels is so constantly present as to be almost, if not absolutely, characteristic. I shall return to this point later.

Observations concerning the elastica in diseases of the vessels are by no means restricted to recent contributions to the literature of vessel disease. Practically all observers working with advancing or advanced lesions in the arteries, and many students of experimental pathology, have directed more or less attention to this phase of the subject. Langhans[76] speaks of indifferently formed elastica in the larger arterial trunks, and growth of new elastic tissue in the vessels at the base of the brain; he also describes

a cellular infiltration of the elastic lamina with the formation of new fibrous tissue. Baumgarten[77] considers the changes in the elastica seen in chronic arteritis and endarteritis, but with special reference to luetic disease of the brain vessels; he described new-formed elastica and broken residual elastic lamina. Eppinger[78] maintains that the primary change in the evolution of aneurysm is rupture of the elastic elements in the media; Manchot[79] holds essentially the same view. Thoma[80] says it is quite clear that arteriosclerosis is dependent upon reduction in the elasticity of vessels, a sort of an angiomalacia, which may be due to functional overdistention, acute and chronic disturbances of metabolism (gout), chronic poisonings (lead, mercury), or specific diseases (typhoid, syphilis). In the later reference he reiterates his views with regard to the relation of widened lumen to proliferative intima, to which I have already referred. Thoma and his school (v. Zwingman,[81] Eberhardt,[82] Mann,[83] Waegner[84]) find the lacerated elastica described by Eppinger and Manchot, but suggest the possibility that the change is physiologic (!) as it may be found in large and small arteries of adults, the newborn, and at intermediate ages. Coats and Auld[85] describe and figure separated elastica, but regard the change as a later manifestation, believing the membrane intact in the earlier stages. According to these writers, the media is affected in atheroma only when the elastica is altered. In one instance they figure broken elastic lamina under an atheromatous patch, and express the conviction that rupture of the membrane of Henle may be followed by inflammatory or reparative changes in the media. Dmitrijeff[86] concludes that in arteriosclerosis there is both disappearance and new growth of elastic tissue; the former, essentially a degeneration, is seen in the early stages, and primarily is marked by changes in tingibility, followed by morphologic alteration and eventually necrosis. The newly-formed elastica, like some other young tissues, possesses less resistance to noxious influences, and hence yields readily before excessive pressure or deleterious bodies. Knox mentions disappearance of the external elastic lamina in the superarterial epicardial fibroid nodules that he describes. Boy-Teissier and Sesques[87] refer to changes in the elastic fibers of the coronary branches in the condition they term xerosis of the heart. Malkoff,[88] in his

study of the relation of trauma to the formation of aneurysm, describes many changes in the elastica, and details the stages of its regeneration. Abramow[89] concludes that the elastic tissue seen in the arteries in syphilitic disease of the vascular system is not newly formed, but results from the splitting of the pre-existing elastica of the inner elastic membrane of the vessels. Herringham[90] looks upon swelling and splitting of the elastica as one of the earliest changes in arteriosclerosis; he thinks regeneration or, at least, new formation occurs. Auld, in the discussion of Herringham's paper, said he had described splitting of the elastica in the arteries of the pia in Bright's disease. Cesaris-Demel[91] describes new formation of elastica in the tunica media of the aorta in aortitis of arteriosclerotic origin. Grohe[92] states that in true inflammation of the arteries elastic tissue is increased, but not in phlebitis; it is formed from pre-existing elastica. In aneurysm there is a reduction in the quantity of elastic tissue, which is fragmented, with curled ends. He observes that the vessels of the brain are especially rich in elastica. Grassmann[93] believes the initial important change in arteriosclerosis is loss of elasticity, which implies of necessity some defect in the elastica. Most clinicians recognize inelasticity as an essential factor of the fully developed disease. Matusewicz[94] describes calcareous changes in the elastic lamina in arteriosclerosis; such infiltration may be seen in normally placed elastica as well as in newly-formed fibers beyond the usual zone. Our knowledge of calcification strongly indicates that it is a regressive process occurring in degenerating or especially necrotic or necrosing fields, and, therefore, its presence in the architecture of a vessel wall constitutes strong presumptive evidence that some retrograde lesion is in progress. I quite agree with Marburg[95] that the hyaline change described by many of the older writers may reasonably be ascribed to change in the elastica; swollen and straightened fibers lose their characteristic stain reaction, and, of course, suffer morphologic alterations. Sections stained by the ordinary routine methods present changes that one would not hesitate to pronounce degenerative, but proper elastic tissue stains at once correct the misapprehension. As Marburg correctly observes, what appeared hyaline by ordinary technic often so appears when treated for elastica, which may be taken as

supporting the view that elastica, as well as fibrous tissue, may be subject to hyaline transformation; intermediate tinctorial reactions also occur. Jores,[96] in his studies of the elastica, describes a fatty metamorphosis of the internal elastic lamina, reacting to Sudan III and also to osmic acid, and also new formation of the elastica in the intima and media of arteriosclerotic vessels. Gilbert and Lion[97] state that the atheroma experimentally produced in rabbits does not differ from that seen in man; they describe the change as a sclerocalcareous transformation; the calcification begins in the elastic fibers, which lose their property of fixing picric acid, become vitreous, thick, brittle, and rigid. At the periphery of the nodule such calcific fibers become continuous with or extend beyond and merge into more or less normal fibers of the vessel wall.

Babcock[98] states that "loss of elastic resistance on the part of a vessel is due to degeneration and atrophy of the elastic fibers of the media, and this destructive change in the middle coat may be due to the long continuance of excessive blood pressure or to sudden, frequent alterations of blood pressure."

In 1900, shortly after the appearance of Weigert's paper,[99] we began, in the laboratories of the Jefferson Medical College Hospital, a systematic study with special reference to the condition of the elastica in a number of conditions. While much of this work has been done by my assistants—for whose cordial co-operation I here express my indebtedness—it was particularly through the enthusiastic labors of Mr. George V. Ridley, a student of medicine, that it was possible to secure comparative study of some twelve hundred sections, stained by the usual routine methods, and especially for elastica. Many of these were from cases of recognized arteriosclerosis and associated with characteristic changes. Others were from patients from whom arteriosclerotic alterations were believed to have been absent, and, as a rule, such belief was corroborated by histologic study. It is quite impossible to review all these cases, as they constitute practically the entire collection of pathologic material accumulated in the laboratory through a number of years. The arteries particularly studied were those situated in the heart, kidney, pancreas, some part of the alimentary canal (stomach or intestine), and lung. In only a small number of instances were

arteries from the muscles available for the study. After the investigation was begun other tissues were added.

I shall cite no specific cases, but give only the alterations most frequently observed. Even in the earlier changes I think it may constantly be recognized that the elastic tissue of the arterioles, and to a lesser degree of the larger trunks, shows, in practically all instances, some more or less marked deviation from the normal. Fragmentation, swelling, separation, and curling of the fragmented ends constitute the most common early alteration.

FIG. 1.

Artery, early stage of arteriosclerosis. Stained especially for the demonstration of the elastica; Weigert's method, followed by Mayer's carmalum and picro-indulin. A. Broken and curled elastica, which at places shows fragmentation. B. Fibrohyaline thickening of the intima; within this stratum can be seen short, crinkled fragments of elastica that have been regarded by some authors as efforts at regeneration. Fragmentation of the elastic lamina is particularly marked just above the leader from letter B. The media in this vessel appears much broader than normal, but it is most difficult, if not impossible, to say that it is hypertrophied.

An arteriole may show but a single break in the elastica, but the retracted and thickened end of the broken fiber usually will be seen clumped and posed like the head and neck of a serpent about to strike. The immediately adjacent laminæ show irregular contortions, often extending beyond their normal limits, as though, in retraction, they had pulled or recoiled out of place. In the relatively early stages the media external to the elastic layer is the seat of no discernible lesion. Just inside the membrane of Henle there is always more or less alteration. (See Fig. 1.) This part of the intima is thickened and reticulated, containing a varying number of round

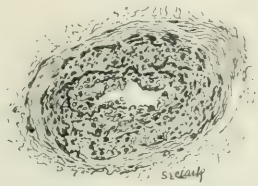
or slightly elongated cells, between which the delicate fibrils of the reticulum are dispersed. In the later stages, within this newly formed fibrous tissue, a varying number of new elastic fibrils can be recognized; as a rule, the latter are short, thinner than those in the normal stratum, and less wavy in contour. The source of these new fibers can be conjectured only; the view that they are parts of or developed from pre-existing elastica may be possible in some instances, but the situation often must be taken as strongly against this view. At what I take to be a later stage (Fig. 2)

Artery, arteriosclerosis. Stained especially for the demonstration of the elastica. Weigert's method, followed by carmalum and picro-indulin. A. Fragmented and separated elastica. B. Fragmented curled elastica; note the swelling of the isolated fragment and the curled end at B. C. Unusually crinkled elastica, resulting from yielding and recoil, due to solution in continuity at A and B. D. From just below the leader from D to upper part of drawing there is no break in the elastica. It will be observed that in that part of the vessel still possessing a practically normal elastica there is no thickening of the intima and subintimal stratum, while the area of altered elastica is overlaid by a fibrohyaline newly formed tissue containing bits of elastic tissue. There is some fragmentation of the external elastic lamina, which is present in this specimen but absent from the arteries, from which Figs. 1 and 3 were made.

the dissociation is more marked, and the fibers appear grosser and less regular in their undulating character. The finely fibrillated subendothelial new formation of fibrous tissue is often more hyaline, and the external elastic lamina, when present, may be the seat of similar changes. The media, that in the earlier stage appeared normal or possibly broader than normal, now seems thinned, often irregularly so, and beneath the areas of fragmented or dissociated elastic fibrils a varying degree of mononuclear infiltration usually can be recognized. This condition has been noted by many observers already mentioned, and commonly is inter-

preted as indicating that the elastica has yielded before the inflammatory process which, in a sense, has permeated or extended into the middle layer. The muscle layer appears to have given way as the result of extension of the trauma, and the accompanying cell accumulations appeal to me as being essentially reparative in nature. New fibrous tissue is in course of production, and with this there is a varying quantity of evidently young elastica, in some specimens very much more than in others. In the more advanced lesion, as affecting the smaller arteries, the dissociation and fragmentation of the elastica, with advanced atrophy of the muscle layer, are most striking. (See Fig. 3.) Little of the normal

FIG. 3.



Artery, advanced arteriosclerosis. Stained especially for the demonstration of the elastica; Weigert's method, followed by carmalum and picro-indulin. In this specimen little more than irregular fragments of the elastica lamina are present. The endothelium no longer forms a separate layer, but, as the result of a proliferative change, the inner stratum is composed of young connective-tissue cells. There may be some doubt as to whether this vessel, during life transmitted blood.

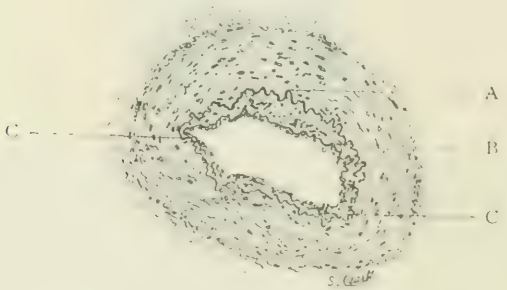
architecture of the vessel remains. The fragments of elastica are but slightly wavy, the irregular separation and distribution most marked, and the whole picture that of dissolution and almost lawless attempts at restitution rather indiscriminately mixed together.

A point upon which additional information especially is desired is the influence of sudden lengthening of the elastica of vessels. Fragmentation in a circular direction can readily be demonstrated, but longitudinal sections of vessels I have studied in a most inadequate manner. There may be evidence of circular splitting and longitudinal dissociation, as indicated in Fig. 4. If my views are correct such appearance could be due to axial stretching, splitting of the elastic lamina, and the two fragments slipping upon each other, while ends (circumferentially considered) remain intact. If a broad rubber band be laid on the flat, one layer upon the other, the two layers can be slid latterly without any great stress on the ends; comparing this crude illustration to a vessel, such splitting

and sliding would probably result in separation and the intercalation of reparative elements between the two parts of the separated lamina, as indicated in the figure.

Between the hurriedly drawn descriptions just given one may recognize myriad kaleidoscopic pictures of intermediate or allied stages that, to one with my own bias of opinion, appear to be manifestations of a lesion primary in the elastica, and characterized by imperfectly evolved efforts at repair. Such efforts are partly in the direction of regeneration of the elastic tissue, and, probably, to a greater degree, a fibrous substitution for a more highly constituted tissue. The regeneration of elastic tissue is admitted by most writers on the process of repair.

FIG. 4.



Split elastica that may have resulted from longitudinal fissuring. A. Outer fragment. B. Inner fragment. C. C. Points where outer and inner fragments join circumferentially. Between the two strata is the usual hyalofibrous reparative tissue.

Even in vessels its growth has been fully recognized by many observers, although perfect restoration is admittedly difficult. Salvia,[99] in his study of vessel anastomosis after resection, shows that nearly complete regeneration is possible, all parts being restored except the elastica. The evolution of elastic tissue in other forms of repair has been fully established, and proliferation of elastica in other pathologic processes widely studied. New elastic tissue in hepatic cirrhosis has been observed by Melnikow-Rasewedenkow,[100] Hohenemser,[102] Jores,[103] Flexner,[104] Oliver,[105] and others. Its production in tumors has been investigated by Melnikow-Rasewedenkow,[106] Williams,[107] Collina,[108] Abel,[109] Federmann,[110] Meinel,[111] Bindi,[112] Ziegler,[113] Hansemann,[115] Hamilton,[114] and others; and unpublished studies made by McKinnie in the

writer's laboratory, are fully confirmatory of the work done by previous investigators. Pearce[115] has shown that the elastica is increased in lungs the seat of chronic passive congestion, and attributes to it the increased firmness of the organ. The studies of Pezzolini[116] on the regeneration of elastica have not been available. In the earlier stages of its evolution elastica must be extremely susceptible to strain, and hence its repair must be beset with great difficulties; I think clinicians are agreed that marked cases of arteriosclerosis reach stages at which they stand still for long periods. In such instances the retrograde changes must be met by some progressive equivalent competent to oppose the continuous stress of the blood pressure. I have seen no evidence of muscle restoration, and, therefore, assume that the elastica meets the demand. Rolleston,[117] in speaking of the law of parsimony, observes that where nature can save the production of such expensive structure as muscle by the evolution of tissue, like elastica, she may do so. Much more is this likely where the production of muscle must necessarily be fraught with insurmountable difficulty. When we consider the constantly changing volume of vessels there is no cause to wonder at the inadequate, even abortive effort at elastica production.

Assuming the hypothesis that the initial change in arteriosclerosis is in the elastica, the question at once arises, What induces it? Roy and Adami[118] have shown that suddenly applied resistance to the onward flow of the blood produces organic changes in the aortic and mitral valves, and edema, sometimes hemorrhages, in the endocardium. Evidently overstrain means tension on the elastica, and overstrain, admittedly a factor in arteriosclerosis, should try to the limit the elastic structures of the vessels. Such excess must be followed by solution in continuity, and this naturally by reparative efforts. Want of adequate nutrition and constant mechanic interference with the process of repair must lead to degenerative change in the formative tissue, and hence the hyaline and necrotic processes constantly observed in these structures. Could anything but strain similarly influence elastic tissue? This is the day of lytic substances, the specificity of whose action is little short of miraculous. Among such bodies may be mentioned the hemolysins, nephrolysins, hepatolysins, myolysins, and many others. Eijkman[119] has shown that certain bacteria evolve

an elastica-dissolving enzyme, and it is not improbable that within our bodies deleterious substances of similar nature may be produced. The assumption that such toxic bodies exist, and that their action is as indicated would lead us a step farther than Thoma's suggestion of angiomalacia, and give what might be termed *elastomalacia* a place of primary importance in the evolution of arteriosclerosis. The foregoing hypothesis might lead us to inquire whether the elastic tissues other than those in the vessels ever suffer in arteriosclerosis? Probably this aspect of the question has not been studied, but the fact that Lancereux found emphysema in 34 per cent. of his cases of arteriosclerosis, and Gull and Sutton note the occurrence of interstitial nephritis in 60 per cent. of the cases of emphysema are observations of more than passing interest. Eppinger believes that the elastic tissue is reduced in emphysema, and the studies of Isaakssohn,[120] and also those of Auld[121] and Sudsuki[122] and others indicate that the elastica is profoundly altered.

I have said next to nothing concerning the very gross and conspicuous lesion commonly termed atheroma, feeling that it is a late stage of arteriosclerosis, and, therefore, not within the scope of this paper. But, as bearing upon changes in the elastica, I should like to call attention especially to that form characterized by the development of grayish-white, wavy, slightly elevated, linear tracings or striæ—mentioned by Moxon over a quarter of a century ago—occurring particularly in the aorta, following the long axis of the affected vessel, and now called linear atheroma.[123] I have had an opportunity to study but one instance of this type, and certainly it strikes one as being a reparative change, essentially a scar, possessing most suggestive differences from the ordinary type of atheroma, with which, however, it may be associated. While not tending to discuss arteritis deformans my conviction is that Hippolyte Martin[124] is correct in laying stress upon the influence of obliterative disease of the vasa vasorum in its production.

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The Earlier Changes in Arteriosclerosis of the Nervous System.*

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It is impossible to make a sharp distinction between the early and late manifestations of arteriosclerosis in the nervous system; there are, however, certain lesions that occur in cases of advanced arterial disease, and are known to every physician; these I shall refer to briefly. Under the late lesions I include areas of extensive softening, secondary degeneration, etc. As life advances, the bloodvessels, especially those at the base of the brain, become sclerotic and often atheromatous, and areas of softening in the basal ganglia, pons, or the white matter and cortex of the cerebrum are not uncommon, and are most frequently produced by thrombosis. Several areas of softening may occasionally be seen in the brains of persons who have passed beyond middle life. Lapinsky[1] has found that with rare exceptions the capillaries of the cerebral cortex are diseased when the large vessels at the base

* Read by invitation.

of the brain are sclerotic, and in such cases the lumina of some of the capillaries are much diminished or even occluded. We are therefore justified in concluding that intense alteration of basal vessels is indicative of alteration of the brain capillaries.

An area of softening in each lenticular nucleus or near the internal capsule of each side, even though small, may cause a symptom-complex known as pseudobulbar palsy; these areas of softening are usually the result of arteriosclerosis.

It is said sometimes that arteriosclerosis cannot be distinguished from syphilitic disease of the bloodvessels. This, I think, is a mistake. Syphilis is a frequent cause of arteriosclerosis, especially when the latter occurs in the young, and in some cases the arteriosclerosis may be a parasyphilitic affection, in the same manner in which tabes dorsalis is a parasyphilitic affection. This form probably cannot be distinguished from other forms of arteriosclerosis. I have seen the brain and cord from many pronounced cases of nervous syphilis, and occasionally have been unable to detect anything abnormal with the naked eye. This absence of macroscopic lesions is not true of every case of syphilis of the nervous system. In those cases in which little or nothing can be detected by the naked eye a microscopic examination probably will show, if the disease be syphilis, thickening of the pia, adhesion of the pia to the spinal cord or brain, round-cell infiltration of the pia or of the walls of the vessels, and possibly miliary gummata arising in the pia and extending into the cord. These are not the lesions of arteriosclerosis, and in this opinion I am supported by Sander,[2] Degenkolb,[3] and others. According to Degenkolb perivascular round-cell infiltration is not caused by arteriosclerosis, but only by infections and intoxications. This view I believe to be correct.

Since the investigations of Charcot and Bouchard, in 1868, miliary aneurysms of the brain have been regarded as the common cause of cerebral hemorrhage. These aneurysms are probably a result of arteriosclerosis. Von Monakow,[4] in speaking of them, refers to the writings of Vulpian, Eichler, Weiss, Zenker, Roth, Arndt, Ziegler, and Löwenfeld, and states that at the present time they are the most probable source of cerebral hemorrhage. Some seem to regard them as the only source of cerebral hemorrhage not traumatic in origin. L. W. Weber[5] reports a case that leads

him to conclude that multiple spontaneous cerebral hemorrhage may occur in severe vascular disease without the formation of miliary aneurysms, and more recently Ferrand has published a thesis in which he ascribes to the lacunes, described by Marie, and mentioned farther on in my paper, a prominent part in the formation of cerebral hemorrhage. I have not been able to obtain his thesis, but in a review of it the statement is made that Ferrand[6] believes the miliary aneurysm is infinitely less common than is usually supposed, and that the common cause of hemorrhage in the brain is the lacune.

The blood pressure is increased in arteriosclerosis by the rigidity of the walls of the vessels and by the contraction of the lumen; therefore any unusual exertion may cause rupture of a diseased cerebral vessel, and it is not necessary to assume that miliary aneurysms exist.

According to L. Jacobsohn[7] the two regions in which arteriosclerosis of the brain is most manifest are the large basal ganglia and the pons, with the medulla oblongata. The investigations of Heubner, Duret, and others have shown that the arteries of the cerebral cortex anastomose, whereas those of the basal ganglia and of the white matter are end arteries, as are also the arteries of the brain stem. The end arteries of the internal capsule and brain stem ascend almost perpendicularly as small vessels coming from much larger ones, and therefore the blood pressure in these small vessels is high. In the pons thrombosis is more common than hemorrhage.

Binswanger and Alzheimer[8] have studied the degeneration of the brain caused by arteriosclerosis. The weight of the brain is diminished, the perivascular spaces are enlarged, the ventricles are dilated, the nerve cells are pigmented, the vessels of the white matter and of the cortex are degenerated and tortuous, and fatty granular cells and blood pigment are found in the perivascular spaces; the glia about the vessels is thickened and spider cells are found, many nerve cells are degenerated, and the medullated fibers are fewer than normal.

In some cases they also found that the arteriosclerosis affects the vessels of the basal ganglia and the brain stem more than those of the cortex. These pathologic alterations cause pronounced symptoms such as headache, vertigo, loss of power of

attention, failure of memory, and mental dulness. In pronounced cases the symptoms are more intense, and dementia may develop.

It seems to me not improbable that impairment of mental activity in advanced age may have some relation to the pigmentation of the nerve cells that increases so markedly after middle life is passed. It would be difficult to prove this, but theoretically we may hold that the large accumulations of pigment masses within the nerve cell must interfere with its function. The term pigmentary degeneration, employed for this process, is, therefore, wisely chosen.

The diagnosis of paretic dementia in the aged should be made with great care. A. W. Campbell [10] has shown that in some cases in which this diagnosis from the clinical side seemed positive the lesions of paretic dementia were not found, and those of senility were present. He was able to observe opacity and thickening of the membranes, increase of cerebrospinal fluid, extreme wasting of the brain and other changes common to both diseases, yet the microscopic features were distinctive, and in addition certain alterations were evident, such as marked chronic endarteritis, embolic and thrombotic softenings, and perivascular hemorrhages with destruction of the surrounding tissue in the basal nuclei and in the pons. These are common changes in senility, but rare in paretic dementia. The symptoms of paretic dementia caused by arteriosclerosis have been observed by others (Binswanger, Alzheimer).

Marie [11] first showed in his large service at the Bicêtre, where are many aged persons, that hemiplegia of the aged is not the result most frequently of cerebral hemorrhage or softening, but of a lacunar process. He expresses surprise that comparatively little attention has been given to this subject. These cavities are of irregular shape, and may vary from the size of a millet seed to that of a large pea, and rarely may be so large as a bean. There may be only one cavity in a cerebral hemisphere, or there may be ten or more in the two hemispheres. They are found most frequently in the external segment of the lenticular nucleus or in the optic thalamus, and not infrequently in the pons. Granular cells are found about these spaces when they are of recent formation. The condition has been described as microscopic softening. In brains in which these cavities are found the bloodvessels are sclerotic ; the pia is moderately thickened ; the convolutions, especially

those of the frontal lobe, are atrophied; the ventricles are dilated; the choroid plexus is often cystic. The vessels of the spinal cord in these cases are sclerotic, and sometimes diffuse sclerosis is found in the posterior columns. It is not senility that causes these lesions, but senility with arteriosclerosis. The cavities are formed by the rupture or closure of small bloodvessels. The transient hemiplegia of the aged is probably caused by the formation of one or more of these small cavities, and this is a subject of great clinical importance.

The état criblé of Durand-Fardel, found in the brain of the aged, consists of many minute cavities in the white matter, of the size of the point or the head of a pin, that are formed by repeated congestion of the bloodvessels. Each cavity contains a bloodvessel, and is a perivascular dilatation.

It is uncertain to what extent senile dementia is caused by arteriosclerosis. Alzheimer says that some authors believe that senile dementia is caused by the atheromatous condition, whereas others think that an hereditary weakness of the central nervous system produces an early atrophy of the nerve cells in association with the malnutrition brought about by the diseased vessels. In a case of presenile dementia that Alzheimer studied, intense atrophic changes were found in the nerve cells, but the atheromatous alteration of the vessels was unimportant. It seems to him possible that the arteriosclerosis of other organs, for example, of the kidneys, may cause alteration of the blood, and in this way affect the nerve cells. This view is disputed.

According to Noetzli, cited by Alzheimer, there is a loss of about two hundred grams in the weight of the brain of the male or female in senile dementia.

Redlich[12] has described a condition in the brains of those who have had epilepsy and senile dementia that he has called miliary sclerosis. Numerous plaques of the size of a ganglion cell, or four to six times this size, were found in the cerebral cortex. They were especially numerous in the pyramidal cell layers. According to Redlich they were derived from neuroglia cells, and contain many fine fibers, although in some plaques the tissue was homogeneous and not fibrillar. Pronounced arteriosclerosis was present in each case. It is uncertain whether this miliary sclerosis is in any intimate relation with arteriosclerosis, but it seems probable that it is.

The explanation that Hirsch[13] gives for optic atrophy occurring with cerebral arteriosclerosis is interesting. Optic atrophy is not rare in this condition, and is caused mechanically by pressure. The optic nerve and the ophthalmic artery pass through the optic foramen in a common sheath. There are cases on record in which the necropsy showed a marked thickening of the artery at this place, in consequence of which the nerve was compressed and atrophied.

Arteriosclerosis produces distinct alteration of the spinal cord. E. Demange[14] has described perivascular sclerosis and minute hemorrhages occurring in the spinal cord in arteriosclerosis, and very recently Pic and Bonnamour[15] have mentioned the finding of similar sclerotic areas, but the lesions in their cases seem to have been slight.

The changes that occur in the spinal cord in arteriosclerosis, according to Sander,[16] are not caused by the contracted kidney, occurring with arteriosclerosis, as some have thought. In the early forms of arteriosclerosis the most intense degeneration may occur in the nervous system, although the general disease is slight. Arteriosclerosis in the kidneys causes changes in the nervous system only in proportion to the marasmus it produces.

In the cases of senility studied by Sander changes were found in the white and gray matter of the cord, and these consisted chiefly in a loss of nerve fibers, especially in the peripheral portions of the lateral columns, with proliferation of the neuroglia. The nerve cells had undergone pigmentary degeneration. The vessels were thickened, and some of them were thrombotic. Round-cell infiltration of the pia or of the walls of the vessels was unimportant.

It seems to me surprising that the changes described by Sander as presenile, and depending on arteriosclerosis, could in some cases be so intense as he pictures. The alteration of the cord, caused by senility according to him, may be the same as that caused by pernicious anemia. I find it difficult to believe that such pronounced alteration of the spinal cord is caused by arteriosclerosis alone, because I have never seen it in the many spinal cords I have studied.

Arteriosclerosis of the spinal cord has been studied in this country especially by Wm. Hirsch. According to him the cells

of the anterior half of the cord are more likely to be affected than those of the posterior part, and this he attributes to the peculiarity of the blood supply of the cord. The anterior spinal arteries are less numerous than the posterior, and the anterior arteries anastomose so as to form one longitudinal vessel on the anterior surface of the cord. The posterior arteries are six in number, and run parallel from the upper part of the cord to the conus. We can readily understand that disease of the anterior arterial supply is likely to be more serious than disease of the posterior supply.

The lower part of the cord, according to Hirsch, is more frequently affected than the upper, and this he explains by the more direct blood supply in the lower region of the cord, and the less protection thereby afforded to the arterioles of the anterior horns in the lumbar and sacral regions against an increased blood pressure.

Motor and trophic disturbances, therefore, are more common than sensory symptoms in arteriosclerosis of the spinal cord, and are more prominent in the lower limbs.

Hirsch[17] believes that arteriosclerosis occurring at the posterior half of the lower part of the cord may, by the proliferation of interstitial tissue, cause a degeneration of the posterior columns, and in this way produce conditions which even anatomically resemble tabes.

Arteriosclerosis is not confined to any one part of the body, but in some cases the spinal symptoms may predominate.

Redlich[18] has found in paralysis agitans in the posterior and lateral columns small islands of sclerosis that had their origin in the vessels, and were therefore perivascular. The small vessels within the white matter have a narrow lumen, because of the thickening of the vessel walls. The arteries of the spinal pia are also thickened. In some places the nerve fibers of the white matter of the spinal cord appear atrophied; in others they have disappeared. In the cervical region the columns of Goll are slightly sclerotic. The nerve cells of the anterior horns are deeply pigmented. Amyloid bodies are numerous. These lesions are regarded by certain investigators, with whom I must agree, as signs of senility, and Redlich also is inclined to regard some of them as of this character. He thinks that the sclerosis of the bloodvessels of the cord is probably a part of the endarteritis

deformans of the larger vessels. The lesions he describes as occurring in paralysis agitans he acknowledges are found sometimes in aged persons who have not had paralysis agitans. He is able to refer to a number of authors who have reported lesions in paralysis agitans like those he has described; and I have seen them in quite a number of cases.

With a knowledge of the existence of these lesions in the spinal cords of certain aged people we can understand the causes of the contractures, especially of the lower limbs, the subjective disturbances of sensation, the changes in the tendon reflexes, etc., that occur in some old people, and that have been studied by Demange, Copin, Gowers, Redlich, and others.

A few words in regard to the changes produced by arteriosclerosis in the peripheral nerves. Some years ago I attempted to obtain evidence that degeneration of bloodvessels produces changes in the nerves of the same territory. I may refer to my remarks made at that time.[19]

Schlesinger[20] says that the primary nature of the vascular disease and the secondary nature of the neuritis are not recognized by all, but he thinks that the vascular alteration occurs first. He reports a case in which pain in the feet and livid discoloration of the feet and hands were followed after some months by gangrene of the left foot. The left foot was amputated, and the arteries and veins of the nerves within it were much thickened. The nerve fibers were normal in many bundles, but in most they were more or less altered and the connective tissue of the nerves was proliferated. He thinks that without doubt the vascular degeneration occurred before the degeneration of the nerve fibers in this case, and he seems to have based this opinion chiefly on the clinical signs, and yet the disease began with pain in the feet as well as with livid discoloration.

When closure of an artery occurs the degeneration of the nerves may be only in the part below the thrombus, as seen in cases studied by Lapinsky. It is not necessary to quote many examples of this. We can accept without dispute the statement that a nerve speedily degenerates when the blood supply is abruptly cut off. Lapinsky says that in cases of acute ischemia he found the changes of the nerve fibers more marked toward the distal ends, where the effects of closure of the arteries were most felt.

The nerve changes were not so perceptible in chronic vascular disease, and, according to Lapinsky, they have been seen in comparatively few cases. In some cases the changes of the nerve fibers were very slight and occurred only in certain areas; in other cases the nerve fibers were well preserved and the connective tissue about them was proliferated: in still other cases the nerves were perfectly normal. Lapinsky has collected the reports of a number of cases from the records bearing on this subject. He observed eight cases of vascular disease; in seven of these the arteries of one lower extremity were affected, and in one the arteries of both extremities were diseased, and gangrene developed in the part imperfectly nourished. The connective tissue of the nerves was increased in all the cases, and this was especially true of the endoneurium.

He concludes, after a careful study of the subject, that chronic endarteritis or arteriosclerosis may cause degenerative changes in the nerves nourished by the diseased vessels; the nerve fibers are very resistant, but the connective tissue proliferates.[21]

Joffroy and Achard[22] seem to have been the first to describe neuritis of vascular origin. In a case of neuritis they found that the most pronounced lesions of the vessels were associated with the most pronounced lesions of the nerves, and from this they concluded that the degeneration of the nerves was due to the thickening and obliteration of their nourishing arteries. Neither this case nor the one published by Dutil and Lamy[23] establishes beyond question the vascular origin of neuritis, although such an origin seems very probable. Dutil and Lamy say that in their case the parallelism existing between the vascular and nervous lesions justifies attributing the degeneration of the nerves to the thickening and obliteration of their nourishing arteries.

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The Early Changes in Arteriosclerosis of the Gastrointestinal Tract.*

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It is with much hesitation and well-grounded fears that I venture to discuss a subject about which there is so little to say. The commoner lesions of the spleen and liver and gastrointestinal tract which are dependent upon advanced arterial disease are already so familiar to you that it would be fruitless to review them.

The subject may of course be regarded from two standpoints. First, there are the changes resulting indirectly from a general arterial sclerosis, combined usually with cardiac disease. Here, the one main factor is chronic passive congestion. Secondly, there are the changes in the different organs which are directly dependent upon disease of the arteries, veins, and capillaries of that particular organ. It is this latter aspect of the subject to which we must confine our attention.

Unfortunately, the early lesions which may follow pathologic alteration in the bloodvessels of the gastrointestinal tract are so slight that their presence can only be detected under the microscope. Under these circumstances clinical manifestations are practically lacking, and it is only advanced arterial sclerosis, with the consequent lesions, which gives any symptoms recognizable during life. Even in the spleen, where, as you know, the blood supply is through terminal arteries, it is not uncommon to see quite a marked endarteritis with hyaline degeneration of the intima unaccompanied by any definite lesions in the pulp. But if a single artery is actually occluded the blood supply is completely shut off from the area nourished by that vessel, and the result is an infarction. So little is known about the function of the spleen that it is impossible to say what the effects of decreased blood supply are upon the general metabolism of the body. They may, of course,

* Read by invitation.

lead to interstitial splenitis, and to atrophy of the organ itself, but since complete removal of the spleen is not incompatible with life, we should certainly expect no serious danger from partial loss of function. Now, whereas partial loss of blood supply may lead to atrophy, chronic passive congestion may produce hypertrophy. In this connection it is conceivable that the recent observations of Dock and Warthin may be of material aid in explaining the interesting and ill-understood condition known as splenic anemia. These authors have described the pathologic findings in two typical cases of splenic anemia which came to autopsy. In both instances the portal vein showed very marked stenosis, and in one case calcification. Only once before apparently has the portal vein been carefully examined in cases of splenic anemia. In this instance the vein was described as narrowed. Although it is possible that the stenosis of the portal vein may be dependent upon the same cause which produces the anemia and splenic enlargement, still the observations of Dock and Warthin are of much interest. Certainly in every autopsy on a case of splenic anemia the portal and splenic veins should be inspected with great care.

When we consider the liver, we find that here, too, early arterial sclerosis is rarely attended by any demonstrable changes in the parenchyma of the organ. Arterial sclerosis and cirrhosis of the liver may and often do occur together, but there is practically no experimental evidence to show that arterial sclerosis is the cause of cirrhosis of the liver. It is much more likely that both conditions are produced by one and the same cause. Alcohol, one of the most potent factors in the origin of cirrhosis, is equally as important in the production of arterial sclerosis. Orth, Welch, and indeed most modern authorities are agreed that thickening of the walls of the bloodvessels in the liver does not alone give rise to cirrhotic changes. Duplaix perhaps is one of the few observers who has upheld the opposite view. It is true indeed that through chronic passive congestion of the liver, a state which may go hand in hand with general arterial sclerosis, new connective tissue may be formed about the central vein of the liver lobules. This condition is well recognized and is usually termed central or cardiac cirrhosis. It has, however, nothing to do with portal cirrhosis. As Cohnheim has shown, the blood supply to the liver is so peculiar that vascular changes which in another

organ would result in grave alterations are here overcome by the infinite capillary anastomoses. To illustrate this fact it is only necessary to mention the extreme rarity of infarction.

In contrast to the liver, arterial sclerosis would seem to play rather an important part in certain diseases of the pancreas. Recent histologic and experimental investigations have gone to show that chronic interstitial pancreatitis is not by any means of rare occurrence. Opie has recently reported the results of a study of thirty cases. He finds that the principal causes of chronic interstitial pancreatitis are occlusion or narrowing of the duct of Wirsung, bacterial infection travelling from the duodenum up the pancreatic ducts, and arterial sclerosis.

Although strictures or compression of the pancreatic ducts are accountable for the greater number of cases of interstitial pancreatitis, arterial sclerosis does play a certain part in other instances. In five out of the thirty cases there was definite arterial sclerosis. In one instance the vascular changes were so striking that they seemed to be the direct cause of the pancreatic condition. The lesions in the pancreas are probably brought about in the following manner: With the narrowing of the vessels the blood supply to the organ is much diminished. This leads to degenerations or atrophy of the highly differentiated cell of the acini, and to subsequent new connective-tissue formation. This series of events, however, does not always take place, for among others Opie has called attention to the fact that marked thickening of the arteries of the pancreas may be present without interstitial changes in the parenchyma.

The close association which has been shown to exist between diabetes mellitus and pancreatic disease naturally renders any study interesting which may have bearing upon this subject. For many years it has been recognized that diabetes mellitus and arterial sclerosis frequently occur together. Such complications of diabetes as gangrene are not infrequently referable to the concomitant arterial sclerosis.

Grube has found arterial sclerosis in 66 out of 177 cases of diabetes; Croner in 32 out of 100; and von Noorden, in his wide clinical experience, has collected 650 cases of diabetes in 261 of which arterial sclerosis was present. Hoppe-Seyler and Fleiner have studied the pancreas in cases of diabetes associated with

arterial sclerosis, and have found in all instances a marked chronic interstitial pancreatitis. In the cases described by Hoppe-Seyler the endarteritis was very extensive, and many of the smaller vessels were almost occluded. Fleiner has noted almost complete disappearance of the parenchyma of the organ with extensive changes in the islands of Langerhans. He likens the condition to the contracted kidney of arteriosclerotics. Opie considers arterial sclerosis as a definite factor in the etiology of diabetes. As an immediate result of narrowing of the pancreatic vessels there are degenerative changes in the parenchyma. Connective tissue readily takes the place of the degenerated cells and later the interstitial changes may even affect the islands of Langerhans. It is now fairly well established that at least some relationship exists between diseases of the islands of Langerhans and certain cases of diabetes mellitus. Through the series of events just described it is therefore possible to trace the connection between arterial sclerosis and diabetes.

A question which has been debated for many years is the influence which arterial disease has in the formation of gastric ulcer. Virchow held the view that the ulcer was due to hemorrhagic necrosis of the mucous membrane produced by thrombosis or embolism of the bloodvessels supplying the mucous membrane. Subsequent observations have given much support to this theory. Openchowski, in cases of round ulcer of the stomach, found extensive hyaline degeneration of the walls of the finer bloodvessels in the margins of the ulcers, and occasionally has noted thrombosis of these vessels by hyaline thrombi. These observations have since been repeatedly confirmed. In one typical gastric ulcer which we have had occasion to study at the Pennsylvania Hospital, practically all the small arteries and even some of the larger vessels in the submucous coat, which formed the margins and base of the ulcer, were plugged by small masses of hyaline material. Their walls were also thickened. The well-known experiments of Panum show very conclusively that ulcers of the stomach may follow plugging of vessels in the submucous and mucous coats. Panum injected wax balls and mercury into the arteries of the lower extremities of dogs, and among other results obtained very definite circumscribed ulcers of the stomach. Cohnheim has produced artificially ulcers which healed with great difficulty in the

stomachs of dogs by injecting chromate of lead into the gastric and splenic arteries. These observations and experiments deal with only one side of the question, and we cannot accept the fact that arterial disease explains with entire satisfaction the etiology of gastric ulcer. As Riegel holds, necrosis of the gastric mucosa brought about by occlusion of the vessels may play a certain role as predisposing factor to the formation of gastric ulcers, but for the maintenance of chronic ulceration he thinks that changes in the gastric secretion are of utmost importance.

Besides the typical round ulcer, other more extensive ulcerations of the stomach have occasionally been described. These were apparently the result of occlusion of gastric vessels. Such a case has been reported by Stockton, who also mentions a similar condition in one of Dr. H. W. Williams' cases.

So little is known about the etiology of duodenal ulcers that the subject can scarcely be discussed in connection with arterial sclerosis. It is, however, possible that the ulceration of the duodenum described, especially by the French, as occurring in uremia may in part be dependent upon arterial sclerotic changes in the intestinal mucous membrane. We have had an opportunity to examine one ulcer of the duodenum which was found at autopsy in a man dying of uremia. There was marked general arterial sclerosis. The ulcer measured about 2½ cm. in diameter, and presented a hemorrhagic necrotic-looking base and margin. It lay upon the head of the pancreas. In sections the margins and base were completely necrotic, and the tissue stained diffusely in eosin. The ulcer extended as far as the submucous coat. In the necrotic base several small vessels were seen which showed extreme thickening of the intima, and, in some instances, thrombosis; the thrombi were composed of masses of hyaline material. Whether this ulcer was directly due to necrosis of the mucous membrane following occlusion of the vessels cannot definitely be decided, but it is possible that such is the explanation of the condition.

Quite recently certain intestinal disturbances occurring in patients who were the subject of advanced arterial sclerosis have been ascribed to endarteritis of the mesenteric vessels. Neusser has reported cases of intestinal distention and colic in angina pectoris. He believes these symptoms may be caused by ischemia of the intestinal wall from occlusion of the smaller mesenteric arteries.

Schnitzler has reported a case of severe intestinal colic the cause of which during life was exceedingly obscure. At autopsy small infarctions of the bowel were found with occlusion of the mesenteric arteries leading to them. Ortner has recorded a case of severe meteorism associated with pain in the region of the umbilicus, in which an autopsy disclosed extreme sclerosis of the abdominal aorta with arterial sclerosis of the mesenteric arteries. For this condition he has suggested the somewhat cumbersome name of "Dispragia intermittens angiosclerotica intestinalis." These observations, though interesting, need further confirmation before we can lay stress on the importance of arterial sclerosis in attacks of colic and intestinal indigestion.

Thus we see that arterial sclerosis does not play a very important part in diseases of liver, spleen or gastrointestinal tract. The main changes are like those in the other organs. As Metschnikoff has aptly said about old age, there is atrophy, degeneration, and death of the noble cells, while their place is taken by the ignoble cells or connective tissue.

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DISCUSSION.

DR. ANDERS said that after having heard the papers he had come to the conclusion that the word "early" as given in the announcement must have been a clerical error. He remarked that he had heard nothing about a good practical division of arteriosclerosis into primary and secondary. The primary was that in which the media and the adventitia were first affected. Afterward a compensatory thickening of the intima followed and led to obstruction, hypertension, and hypertrophy of the heart. In the secondary stage there was a primary condition of hypertension, causing dilatation of the vessels, slowing of the current, and com-

pensatory thickening of the intima. A division into nodular and diffuse was also of practical value. The speaker was impressed with the belief that in some of the cases reported in Dr. Spiller's paper nodular arteriosclerosis of the brain must have existed. This, he said, started in the vasa vasorum and led to great thickening in local areas, with obstruction, while diffuse arteriosclerosis was rather a general condition. In the majority of cases the lesions in the latter variety were more marked in some organs of the body than in others or parts of organs, even. He was much interested in arteriosclerosis in kidney disease, but thought that Dr. White should have laid more stress upon the atrophic changes in the muscular coat of the arteries. He believed that arteriosclerosis in the kidney was in many cases associated, even in its early stage, with coronary sclerosis. The subject of the elasticity of the blood-vessels interested him. This was not lost in the early stage, nor even altogether in the advanced stage of arteriosclerosis, but a distinction between arteriosclerosis and atheroma should be made. The elasticity of the vessel was, according to Roy, greatest when the pressure was normal. Hypertension aggravated any defect in the elasticity of the vessel wall.

The effect of arteriosclerosis was to narrow the lumen of the blood-vessels. This brought up the question of the changes in the blood supply of the organs. We should study whether arteriosclerosis and lesions of the liver, spleen, and pancreas stood to one another in the relation of cause and effect. In the case of the pancreas, this relation, as pointed out by Dr. Longcope, was established; but it was difficult to comprehend why arteriosclerosis should be more responsible for disease of the pancreas than for that of other organs. Dr. Anders had never seen disease of the digestive tract for which no contributory cause could be discovered associated with arteriosclerosis. In conclusion, he said that it was difficult to recognize the early stages of arteriosclerosis.

Dr. Daland was interested in the papers, but said that one important cause of arteriosclerosis had been omitted, viz.: excess of mental work. He recollected a considerable number of cases in his practice in which this had been a factor; and he believed that it played an important role, especially in America, in producing arteriosclerosis. He thought that there was, especially in overworked neurasthenics, for a number of hours during each day, an arterial

contraction, and that this, if continued for months or years, brought about arteriocapillary fibrosis. He related the case of a girl of nine years who had been poisoned with Worcestershire sauce, and had pharyngitis, gastroenteritis, catarrhal nephritis, convulsions, coma. Examination later showed cardiac dilatation and a mitral systolic murmur, with well-marked thickening of the arteries. Within a week the arterial thickening diminished and the murmur had disappeared, and it was concluded that the condition was one of arterial spasm. Dr. Daland thought that atheroma was often the end-process of arteriocapillary fibrosis. He believed that, as had been stated, some persons are born with weak material in the make-up of their vascular system. He was interested in the hypertrophy of the glomerulus referred to by Dr. White, as it reminded him of hypertrophy of the left kidney in connection with hydronephrosis of the right kidney, due to complete obstruction of the ureter caused by a calculus. The pathologic appearance suggested that the complete and total obstruction of the ureter had existed previously, and that the enlargement of the left kidney was merely compensatory.

Dr. McCarthy said that he was interested in arteriosclerosis of the nervous system. He believed that only when the sclerosis was advanced were there recognizable pathologic and clinical manifestations. Miliary aneurysms were not common, but nodular conditions were nearly always present, especially at the points at which small vessels left large ones. Embolic softening was more common in the great brain than elsewhere. Thickening of the vessels was usually associated with dilatation, particularly in vessels taking a sharp turn. In no part of the body could arteriosclerosis be so far advanced without producing symptoms as in the brain. In tuberculosis, arteriosclerosis was frequently found at the base, but did not seem to produce symptoms.

Dr. Spiller said that in arteriosclerosis of a mild degree there might be no symptoms, but headache and vertigo were not uncommon as early signs of arteriosclerosis. Most pathologists agreed that areas of softening were not found so frequently in the pons as in the region of the basal ganglia. He doubted whether miliary aneurysms were so common as was stated, although he was certain that they did occur.

February 25, 1904.

Proceedings

of the

Pathological Society of Philadelphia.

JUNE, 1904. NEW SERIES, VOL. VII., NO. 6.

TABLE OF CONTENTS.

LOEB and SMITH, The Presence of a Substance Inhibiting the Coagulation of the Blood in Anchylostoma.—COPLIN, Carcinoma of the Esophagus.—FRANCINE, Eight Cases of Aneurysm of the Innominate Artery.—EDSALL and ROBERTSON, A Case of Post-pneumonic Endocarditis.

The Presence of a Substance Inhibiting the Coagulation of the Blood in Anchylostoma.

LEO LOEB, M.D., AND A. J. SMITH, M.D.

(From the Pathologic Laboratory of the University of Pennsylvania.)

The possibility of the existence of a substance inhibiting the coagulation of the blood in such parasitic worms as the anchylostoma suggested itself to the writers independently—to one of us from former experimental studies on the action of leech extract on the coagulation of the blood,[1] and to the other from clinical and pathologic studies on Uncinaria americana.[2] The suggestion that in many, perhaps all, blood-sucking animals such substances existed had already been made by Sabbatani,[3] who discovered the presence of such an agency in Ixodus ricinus. Recently it had been mentioned as a possibility by one of us[2] in the case of anchylostoma. It was, however, necessary to give an experimental proof of the actual existence of such a substance, and we therefore decided to undertake experiments on Anchylostomum caninum, which we could procure much more easily than Anchylostomum duodenale or americanum, and which could be obtained in a sufficiently fresh state, a condition only with difficulty fulfilled in

the case of the human anchylostomum obtained at the autopsy. The close resemblance of both varieties of anchylostoma render it permissible to apply facts of such a nature found in one kind of parasite to the other.

It seems of especial pathologic interest to prove the existence of this substance in anchylostoma, because the anemia of the host following an infection with these nematodes is very marked. Although a number of factors have been suggested as the cause of this anemia, as, for instance, an hemolytic or otherwise toxic action of secretions of the parasite, or the effects of the multiple ulcerations of the intestines favoring an absorption of toxic substances from the intestinal canal, or the simple effect of the loss of blood through the blood-sucking of the parasite, a real proof of the existence of one of these factors has so far not been given. The effect of a substance which inhibits the coagulation of the blood would certainly be of some importance as at least a contributory factor causing the anemia. The blood-sucking alone might not be sufficient to account for the resulting anemia, especially if the view recently expressed by Looss[1] will be shown to be correct, namely, that the intestinal mucosa, and not the blood, forms the proper nutriment for the parasite. However, we find, certainly in the intestines, many anchylostoma filled with blood. The loss of blood will be considerably increased if, after an injury of the mucosa or submucosa, the oozing continues for some time. That this takes place has been observed by many investigators. Occasionally a considerable quantity of blood has been found in the intestines. The importance of this factor is increased by the circumstance that the worms, especially at certain periods, frequently change their place, and that we therefore are apt to find many more places of injury than we should expect from the number of parasites present.

The significance of the presence of such a substance becomes especially apparent if we take into consideration the fact found by L. Loeb in the course of experiments on tissue coagulins, that the intestinal mucous membrane and the mucus covering the intestinal mucous membrane have a very strong effect in accelerating the coagulation of the blood. Without the presence of a counteracting substance as the one found by us in anchylostoma, it is very

likely that a bite of the parasite would not be followed by after-bleeding.

The experiments were carried out in the following way: The worms were removed from the intestinal canal of a narcotized dog, and received in a dish containing 0.85 per cent. sodium chlorid solution. In order to wash off any adhering parts of the intestinal contents, they were transferred to a second dish also containing salt solution. Following this they were ground up in a small mortar by adding a small amount of powdered glass and a measured quantity of 0.85 per cent. sodium chlorid solution. The active substances were then extracted in the ice chest during several hours or overnight.

The extract was distributed into several test-tubes, 1 c.c. of the extract into each tube. In other tubes an equal amount of an 0.85 per cent. sodium chlorid solution was introduced as a control. Through a canula blood was obtained from the femoral artery of a dog, and 1 or 2 c.c. of this blood was directly received in the test-tubes and well mixed with the solution. The time of the beginning and finished coagulation was then determined.

In four dogs we found what we believed to be a sufficiently large number of anchylostoma for carrying out these experiments. In one case we found 135, in the second 100, in the third 27, and in the fourth case we found 85 animals. The third experiment, in which we had only 27 worms at our disposal, did not give any pronounced results; the number of animals used was probably not sufficient, or the animals had been standing too long before the experiment was made; in the other three experiments, however, we obtained very clear results. In the control tubes containing sodium chlorid solution the blood coagulated in between 5 and 9 minutes; in the tubes containing the extract coagulation was delayed for many hours, and in a number of cases for 24 hours and longer.

In experiments in which we cut the anchylostoma in the center of its body and prepared extracts from the anterior and posterior parts of the body separately, we found that the posterior half contained no coagulation inhibiting substance, or only very little of it, that the anterior part alone contained a large quantity of the active substance. Perhaps the small amount which in one experiment

could be found in the posterior part may be accounted for by the animal swallowing some of the material, in which way it might easily be carried into the posterior half of the digestive tract.

In regard to the seat of the production of this substance in the anterior part of the body we cannot make any definite statement. In the leech it is produced in the monocellular pharyngeal glands. In the anchylostomum we have, according to Looss,[5] to distinguish among three kinds of glands: the head, esophageal, and cervical glands. The cervical glands opening into the excretory system of the animal are very unlikely to produce this substance. Looss seems to believe that the toxic substances of anchylostoma are secreted in the head glands. In his recent paper A. J. Smith had suggested that the esophageal glands secreted the toxic substances, the paper of Looss having not yet appeared at that time. It is very probable that the coagulation inhibiting substance is either produced in the head or the esophageal glands.

The active substance present in the leech is not destroyed by boiling it for some time. On the other hand, Sabbatani found that the substance present in ixodes is destroyed by boiling it ten minutes. We found that boiling fifteen minutes does not entirely destroy the coagulation inhibiting substance of anchylostomum, that however it weakens it markedly.

That the presence of such a substance is not common to all intestinal parasites we found in control experiments carried out in a similar manner with Ascaris mystax and with a tenia found in a dog. Extracts of both these animals showed the opposite effect; they accelerated the coagulation of the blood. The substance found in lumbricus by L. Camus and P. Lequeux,[6] which inhibits the coagulation of the blood after intravenous injection, is of an entirely different kind, being much more comparable to the action of peptone than to that of the leech or the anchylostomum.

In the course of these experiments we had an opportunity of making some observations on the behavior of the red blood corpuscles of the dog in the extracts of Anchylostomum caninum. We found on the whole the blood corpuscles microscopically well preserved after six hours. After seventeen hours, standing at room temperature, the mixture of the blood plasma and extract was still clear and did not indicate any marked hemolysis. The anchylos-

tomum extract behaves in this respect in a way similar to that of the leech extract. It is, therefore, unlikely, that these parasites cause anemia by the direct production of a hemolytic toxin.

Conclusion. In the anterior half of anchylostomum there is present a substance markedly inhibiting the coagulation of the blood, which, in a similar way to leech extract, acts in vitro. It is not entirely destroyed by boiling. A hemolytic action of the extract of anchylostomum cannot be demonstrated. The substance inhibiting the coagulation of the blood is probably a factor contributing to the anemia which is so frequently the result of an anchylostomum infection. *May* 12, 1904.

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DISCUSSION.

DR. STENGEL said that he had noticed a viscous condition of the blood when mixed with leeches' heads. He also remarked that when looking up ankylostoma-anemia some years ago he had found pernicious anemia to have occurred when there were but few worms. His conclusion had been at that time that the anemia was not due to the abstraction of blood, but he was now prepared to admit that this conclusion was less certain than he then believed. He also believed that the anchylostoma shifted its ground.

DR. COPLIN said that Dr. Kiefer had shown to the Society a specimen of attached anchylostoma from the Phlippines. There was a relatively large number of punctures in the intestines in anchylostoma-anemia as compared with the number of parasites. Great regenerative capacity was required to meet the constant small waste.

DR. LOEB, in closing, stated that he had not observed stickiness of the blood. Dr. Smith, he said, was more competent to discuss the clinical side. They were not prepared to say that hemorrhage was the only cause of the anemia. The absorption of bacterial toxins might be a factor. The action of pepsin as a cause of lessened

coagulability of the blood was excluded by the division of the parasites into two parts, and also by the fact that peptone does not act in vitro. They had also made experiments with the ascaris, as it had been shown that the liver and the pancreas of many invertebrates contained substances inhibiting the coagulation of invertebrate blood.

Carcinoma of the Esophagus.

W. M. L. COPLIN, M.D.

(From the Laboratories of the Jefferson Medical College Hospital and the Philadelphia Hospital.)

Tumors of the esophagus are not of common occurrence. Of the benign neoplasms fibroma is the most frequent: it may be in the submucosa, interstitial or polypoid. Rarely the polypoid or pedunculated fibroma is so situated that it may be vomited or regurgitated into the pharynx and give rise to symptoms of suffocation, relieved by swallowing. Rokitansky[1] reported a smooth, lobulated fibroma seven inches long and two and one-half inches wide. Sarkisoff[2] reports a fibroma of the esophagus that underwent necrosis and was vomited; the patient recovered. He thinks the tumor was located near the sixth dorsal vertebra. A few cases of myoma, lipoma and adenoma of the esophagus have been recorded. Such tumors, however, are very rare.

Howard[3] reports a primary sarcoma of the esophagus with metastases to cardiac end of stomach. In individuals under twenty-five years sarcoma is more common than cancer. It usually involves the lower third of the organ. Of 12 reported cases of sarcoma of the esophagus most were in males; 9 of the 12 were in the lower half of the organ; the tumor usually surrounds the lumen, but in 3 cases it was pedunculated or polypoid.

There were symptoms of obstruction in 11 of the 12 cases; perforation or involvement of respiratory organs occurred in 4. All varieties of sarcoma except angiosarcoma have been reported: 25 per cent. are of the round-cell variety. Metastases were present in 5 of the 12 cases, and in 2 the metastases were widespread.

Sarcoma of the esophagus runs a more rapid course than cancer. Since the publication of Howard's paper, v. Eicken[4] has reported a spindle-cell sarcoma of the esophagus.

Carcinoma of the esophagus usually is regarded as rare, even when compared with cancer of other parts of the body. Of 7290 cases of cancer collected by Williams, 2669 were in men, and of these 5.3 per cent. were primary in the esophagus. Of 4628 cases of cancer in women the primary lesion was in the esophagus in 0.7 per cent. (35). Kraus[5] does not think cancer of the esophagus so rare as is usually held; he gives the esophagus about the fifth place among the organs in which carcinoma occurs. Tanchon[6] in 9116 cases of cancer found 13 of the esophagus and 2303 of the stomach.

Although a disease of advanced life, it is not unknown in the young; Heiman[7] recorded a case in a patient of nineteen years, Stewart,[8] twenty-three years, and Harris[9] in a man aged twenty-one years. The great mass of patients are past forty, and 35 per cent. of them between fifty and sixty years of age. The great preponderance of patients are males; of 772 cases of esophageal cancer collated by Kraus 584 were males; but 12 of Butlin's[10] 59 patients were women; Rolleston[11] states that of 55 cases of carcinoma of the esophagus collected by Wilson from the postmortem books of St. George's Hospital, 8 were women, and of 510 cases gathered by Newmann 108 were women. Women are attacked earlier in life (about the forty-fourth year) than men (about the fifty-fourth year) (Butlin); of Emanuel's 6 cases 5 were men between fifty-one and fifty-five years, and 1 a woman aged thirty-three years.

The exciting cause of cancer of the esophagus, like cancer in general, is as yet not known. Many predisposing factors have been given more or less importance, some of them clearly more than they deserve.

In this article it is not the writer's purpose to include cancer of the esophagus resulting from metastases or direct extension, but mention should be made of those rare cases of esophageal carcinoma resulting from involvement of the organ by tumors arising in the pharynx, tongue, or stomach. That trauma or irritation of some kind may have something to do with the development of

esophageal cancer is indicated by the fact that such growths are most frequent where the organ is most exposed to insults from bodies during their transmission through its lumen. Zenker[12] thinks it may depend on chemical, thermal, or mechanical irritation. All writers lay some stress on alcohol as a possible cause. Körner,[13] Voelcker,[14] and Leberts[15] suggest that it is favored by the mechanical irritation resulting from enlarged periesophageal or peribronchial glands. Ritter[16] thinks an esophageal diverticulum may constitute a point from which cancer can arise. Henoch,[17] Kraus, Dieninger,[18] and others attribute a certain influence to hot foods or bolting large boloses. Wendland,[19] Fritsche,[20] and others have implicated hot or cold draughts. Ritter[21] thinks a traction diverticulum may constitute a point of lessened resistance in which carcinoma may arise. It is easy to appreciate that any pouch or "silent area" in which food could lodge or other irritants prolong their action might be similarly disposed. Leberts found a plum-seed in a carcinoma, and suggests that such foreign bodies may be causes. Röpke[22] reports an esophageal carcinoma developing out of a scar. Wolf[23] reports 2 cases of carcinoma of the esophagus associated with spondylitis deformans, briefly records a third case observed by Orth, and states that Schmorl knew of 2 additional cases.

With regard to location authorities are not agreed. J. Solis Cohen[24] does not think that any particular division of the esophagus is especially prone to the disease. Recklinghausen taught that cancer of the esophagus was most common where the organ is crossed by the left bronchus. Similar views were held by Virchow,[25] Harrison Allen,[26] Zenker,[27] and Klebs, Rindfleisch, König and some other text-book writers.

In 901 cases collated by Kraus 44 involved more than one part of the organ; 397 were in the lower third, 302 in the middle, and 158 in the upper third. Von Hacker in 131 cases found 13 in the neck region, 53 in the neighborhood of the bronchial bifurcation, 36 in the hiatus, and 29 at the cardia, making the numbers for the various thirds, from above downward, 13, 53, and 65 respectively. Butlin observes that if the esophagus be divided into upper and lower halves the tumors will be fairly equally distributed in the two points. In Newmann's[28] 445 cases, 227 involved the upper

part of the esophagus, 120 were situated in the lower and 98 in the middle third. According to Gross,[29] the most frequent site is behind the larynx. Osler[30] says the upper third, and Pepper,[31] in order of frequency, names the region of the cardia, bronchial crossing, and cricoid area; Zenker and v. Ziemssen agree with Kraus and v. Hacker.

With regard to the type of cancer, all records show that squamous-cell epithelioma is by far the most frequent; other types of carcinoma of the esophagus are exceedingly rare. Butlin's cases consisted of 54 squamous-cell, 3 scirrhous, 1 medullary, and 1 colloid. The colloid spoken of by Butlin, and one observed by Eppinger,[32] are exceptional. The adenocarcinomas are usually at or near the cardia; they may be extensions from primary growths in the stomach, or possibly some of them arise from ectopia of gastric glandular elements abnormally placed in the lower part of the esophagus. Of the origin of esophageal cancer from glands in the mucosa too little is known to justify any sweeping deductions.

Anatomically, cancers of the esophagus assume many forms. Papillary growths, irregular projections, polypoid masses that may or may not be lobulated, bossed or fissured, infiltration of the wall of the tube tending to encircle, but rarely doing so, and irregular linear masses which may or may not ulcerate, constitute the most common forms: Kraus cites cases in which all but a few centimeters of the tube was involved. In other cases, as in the one reported in this paper, large nodular masses develop attached to the esophageal wall by relatively narrow stalks; this type ulcerates slowly. It may give rise to marked obstruction that disappears with the advent of necrosis, even before destructive ulceration approaches the esophageal wall. This misleading clinical phenomenon is particularly remarked upon by Arnold.[33] Ulceration was absent in but 5 of 54 in Butlin's series, and in 3 of the 55 St. George's Hospital cases. Isolated patches of ulceration occur In types not taking on this polypoid character or having assumed that form, and later by necrosis lost the external projection, and finally invaded the esophageal wall, stenosis may be brought about by infiltration, or, what is more common, the coincident increase in fibrous tissue associated with contraction may narrow the tube. As a result of the obstructive lesion there is commonly

an initial hypertrophy of the esophageal musculature sooner or later, followed by wasting and dilatation. The more or less relaxed organ may assume a spindle form, but usually the cavity created by gradual distention is largest just above, but not immediately at, the obstruction, and from this point of maximum width progressively narrows to approximately the normal size at the upper limit of the organ. Of course, the lower the tumor and, other things being equal, the slower stenosis develops the more capacious the sac may be. In some instances fluids and solids may accumulate in such quantity that the consequent regurgitation appears, from necessity, to be a true vomiting of gastric contents. Such dilatation may occur without demonstrable stenosis at autopsy, but, as Rolleston indicates, the differences between functional obstruction and demonstrable anatomic narrowing may be quite marked.

Some of the complicating anatomical changes are of great clinical interest. Cancer of the esophagus tends to involve the peribronchial and mediastinal lymph-nodes, the gastric glands, the air-passages, and the adjacent bloodvessels and lungs, the thyroid and less frequently the pleura, pericardium, and heart. When the lung is penetrated, Rolleston observes that it is usually the right organ that is involved.

Treves[34] reports a case of carcinoma of the lower end of the esophagus involving nearly the whole length of the lesser curvature, the patient surviving a gastrostomy (at which time the diagnosis, based on symptoms, was verified) for two years and eleven months. Fütterer[36] reports a case where cancer of the stomach depended upon transplantation from a growth in the esophagus. He collected 6 similar cases from literature. Kraske has reported 2 instances of cancer of the rectum with transplantation below. When the esophagus is perforated by the growth the trachea may be involved; in Zenker's 120 cases of perforation the air-passages were affected in 70; in 26, 1 bronchus, and in 21 the trachea was entered; in 27 the right lung, and in 6 the left was affected. In Homan's[36] case there was an external opening and also perforation of the trachea.

Adenot and Cadet[37] report cancer of the esophagus with esophagotracheal fistula and gaseous distention of the stomach

by air thought to have passed through the trachea into the esophagus, and in that way into the stomach. Gastrostomy was done, at which time the stomach was found distended, and the organ filled and emptied during respiration in such a way as to render the operation more difficult. Three centimeters above the tracheal bifurcation, exactly in the median line posteriorly, there was a mammilated projection into the trachea that contained an opening communicating with the esophagus. Sirot[38] has been able to collect 68 cases of esophagotracheal fistula. Adenot and Cadet do not state whether these were all cancerous or not, and the original paper has not been available for examination. Since the publication of Sirot's thesis a number of cases have been reported; the complication is not infrequent. In nearly all cases of cancer of the esophagus where the stomach has been observed at operation or autopsy the organ is small, retracted, hidden under the liver, difficult to find, and, at operation, surgeons have opened the colon instead. Adenot and Cadet think that in their case, during inspiration, air passed through the fistula into the esophagus, and in expiration it was forced onward into the stomach, where it accumulated. They, therefore, hold that where a tracheo- or bronchoesophageal fistula is suspected, the stomach should be percussed with care to determine if there is any undue distention of the organ caused by aerophagy. Cadet and Revol[39] and a few other observers have reported cases in which esophagotracheal fistulas secondary to cancer of the esophagus were entirely latent.

Ross[40] reports a cancer of the esophagus involving the vertebræ and producing paraplegia.

Bureau[41] reports a cancer of the esophagus adherent to left auricle in which was a nodule, the size of a pea, situated just under the endocardium. There was a stenosing growth of the esophagus, with ulceration and perforation into the middle lobe of the right lung. The sputum was fetid, and a pleural effusion amounting to 500 c.c. was present. The patient had vomited some blood on one occasion. The muscle fibers of the heart were atrophied and infiltrated by cancer cells; the left pulmonary vein and the pneumogastric were compressed by the growth, which was an epidermoid cancer. Tachycardia (160) was present.

McKendrick[42] records an epithelioma of the upper part of the esophagus, with involvement of the pneumogastric and including both recurrent laryngeal nerves; the symptoms—slight dysphagia, dyspnea, stridor, cough, and aphonia—indicated aneurysm of the aorta. Kuckein[43] reports 2 similar cases both diagnosed as aortic aneurysm, and in both expansile shadows by the X-ray were produced, due to the pressure of the filling aorta upon the tumor.

Saundby and Hewetson[44] report an extensive carcinoma of the esophagus occurring in a man aged fifty years. He had been ill three years. There were enlarged glands in the neck and around the aorta, the latter involving both vagi and the recurrent laryngeal nerves; edema of the lungs, consolidation and secondary deposits at the base were also present. The upper part of the esophagus for six inches was involved in a sloughing malignant growth which projected into the lumen and bound the esophagus to the trachea which at one point was perforated. The growth extended from the first ring of the trachea to three inches below the bifurcation, a distance of six inches. The lumen of the esophagus between these points was three times the normal size; there was no stricture at any point. The growth extended completly around the esophagus and over points involved the whole thickness of the wall. The broncholymphatic glands were affected. The trachea was compressed and a button-like mass extending into the left bronchus. The pneumogastric nerves were involved on each side just behind the bronchi. The growth was a spheroidal-cell carcinoma; cell nests were absent in both primary and secondary growths. The difficulty in swallowing depended not upon stenosis but involvement of the musculature of the esophagus. Fluid gravitated into the stomach better than solids, hence the appearance of stenosis. The sudden attacks of vomiting appeared to depend upon involvement of the pneumogastric nerves.

The tendency of such tumors, when located in appropriate regions, to involve, usually by inclusion, any adjacent nerves may account for the occurrence of bradycardia or tachycardia, both of which have been observed repeatedly. Compression of a degree sufficient to stimulate the pneumogastric would slow the heart, and stimulation of the fibers coming from the inferior cervical

sympathetic ganglion would accelerate, and possibly in these facts may be found a satisfactory explanation for the occasional tachycardia and bradycardia. The latter was present in Arnold's case, the pulse for two months ranging between 50 and 60.

Carcinoma of the gullet may be latent; Hödlmoser[45] reports 2 such cases. In both dysphagia was absent, and there were no esophageal symptoms. Unilateral paralysis of the recurrent laryngeal nerve was the most marked symptom. Some enlargement of the subclavicular glands was present, and in one case the tumor was attached to a tuberculous gland.

Emanuel[46] records 6 cases of cancer of the esophagus without obstruction. In 2 of his 6 cases infiltration and perforation of the trachea occurred; in 3 the left bronchus was perforated; in 1 case the growth was low and penetrated the lung. Cough or other respiratory disturbance coming on immediately after swallowing should be regarded as a symptom of laryngeal or bronchial involvement.

Dickinson[47] reports a case in which penetration of the subclavian artery occurred. S. Jones[48] records an instance of perforation of the intercostal arteries, with fatal hemorrhage. Taylor[49] has been able to collect 9 cases of ulceration into the aorta or its branches.

With regard to the life-expectancy in these cases, much depends upon the intervention of the surgeon who may, by gastrostomy, prolong life. Rolleston states that most patients die within a year of the appearance of symptoms, that carcinoma of the upper part of the esophagus is more rapidly fatal than when the lower third is involved, and scirrhous carcinoma progresses less rapidly than the squamous-cell variety. The last statement is not in harmony with our knowledge of the two varieties of cancer when occurring elsewhere. Pepper's observation that metastases is less frequent than in carcinoma of other organs is correct if we exclude certain feebly malignant epitheliomata involving the skin.

Diagnosticians will find no little difficulty in differentiating esophageal malignant stenosis from other forms of narrowing, and these difficulties will not be lessened by the findings of Soupault,[50] who records 4 cases in which the symptoms resembled stricture of the esophagus, but were due to atrophic retraction of stomach, small retracted organs being found at autopsy; 4 similar cases are

found in literature. Von Cackovic[51] reports 2 cases of total contraction or shrinking of the stomach. In such cases the symptoms and even the results of instrumental examination may closely resemble stenosis, and hence carcinoma of the esophagus.

With regard to the treatment little can be said. Radical operative procedures directed to the neoplasm have proven disastrous, but gastrostomy or other palliative undertaking usually is regarded as most valuable. Recently Exner[52] has treated esophageal cancer by the use of a tube of radium attached to the end of an esophageal bougie; the capsule containing the radium should have the diameter of a No. 16 bougie. He reports 3 cases in all of which there was lessened stenosis, but as this may result from sloughing independently of any so-called resorptive action the observation offers at present no conclusive evidence of specific benefit.

The following is a brief summary of the postmortem findings in a case of carcinoma of the esophagus coming to autopsy in the Philadelphia Hospital. The patient was under the care of Dr. Thomas G. Ashton, who will report the clinical details elsewhere:

H. McG. (Men's Medical Ward). Patient male, white, aged sixty-three years, native of Ireland. Admitted August 27, 1903, died January 26, 1904; autopsy held January 26, 1904.

Pathologic Diagnosis. 1. Visceroptosis. 2. Chronic adhesive pleuritis (sinistra). 3. Healed-in pulmonary tuberculosis. 4. Atrophy of heart. 5. Arteriosclerosis. 6. Chronic interstitial nephritis. 7. "Polypus" of esophagus. 8. Catarrhal gastritis. 9. Atrophy of liver. 10. Meckel's diverticulum.

Body is that of an emaciated, aged male; marked atrophy of the muscles; scaphoid abdomen; over acromial end of both scapulæ are endosseous nodes irregular and plate-like, extending downward along the spines. Subcutaneous fat is scanty, almost wanting. Musculature pale, flabby, wasted.

Abdomen, marked splanchnoptosis; all of the small intestines lying in the pelvis, transverse colon on brim of pelvis. Duodenum just under umbilicus. Liver also prolapsed. Stomach nearly vertical.

Thoracic Cavity. Left pleura uniformly adherent with old firm, fibrous adhesions. Right pleura adherent only at the base poste-

riorly. Pericardium contains 100 c.c. of clear, straw-colored fluid. Serosa normal. Subepicardial fat is gelatiniform. Right ventricle contains small quantities of coagulum. Right auricle capacious and distended with clots. Left side empty. Auriculoventricular orifice on right side dilated, transmits four fingers and thumb. Valves of right side normal. Marked thickening of mitral leaflets, atheroma of valve bases. Aortic leaflets slightly stiff; no marked valve lesions. Coronary arteries tortuous, typical pipe-stems at places. Atrium of left coronary artery stenosed. Myocardium brownish, firm, contains small grayish areas. Heart weighs 250 gms. Aorta atheromatous.

Lungs. Both organs show some changes; a few old cretaceous areas 0.25 by 0.5 cm. in diameter. Similar changes in peribronchial glands. Bronchi normal. Larynx and trachea show no gross lesions. Left lung weighs 500 gms.; right lung weighs 520 gms.

Spleen normal in size and color, slightly fibrous, contains numerous cretaceous nodules 2 to 5 mm. in diameter. Parenchyma slightly edematous and somewhat congested. Malpighian bodies rather inconspicuous. Weight 120 gms.

Left adrenal slightly enlarged, contains many small cretaceous tubercles

Left Kidney. Cortex narrow, firm, capsule adherent, surface granular, resists incision, considerably congested, but not small in size.

Pelvis and *ureters* normal. Right adrenal and kidney in condition similar to the left. Right kidney weighs 150 gms.; left, 160 gms.

Bladder contracted and empty. Middle lobe of prostate slightly enlarged Internal and external genitals normal.

Duodenum normal. Biliary passages patulous. Gall-bladder distended with 250 c.c. of rather thick bile containing considerable biliary sand.

Liver slightly fibrous; capsule thickened, adhesions around gall-bladder. Organ rather soft and flabby, but resists incision. Weight 1570 gms.

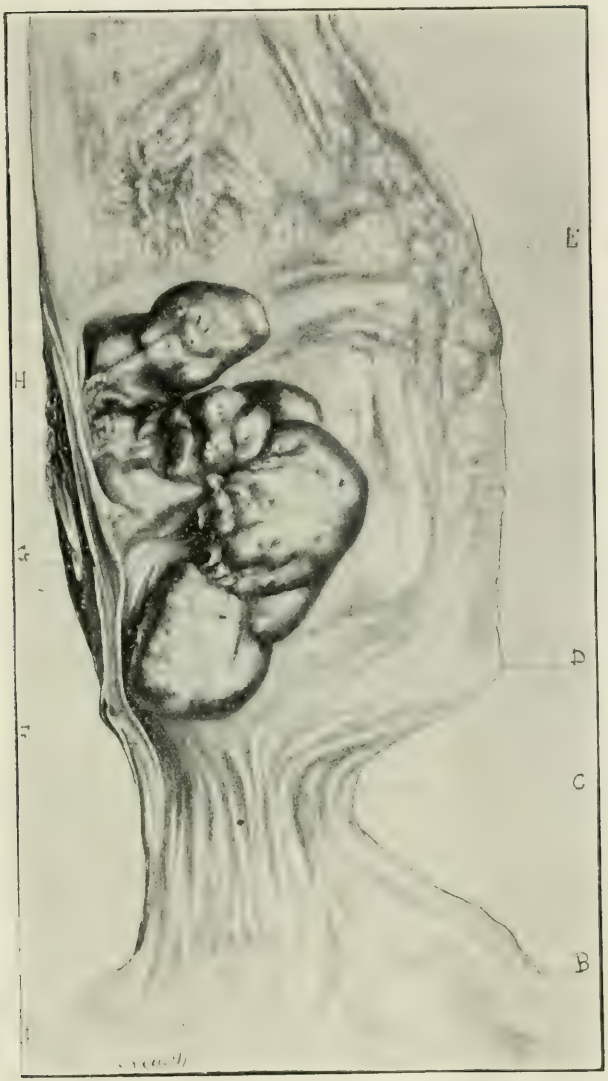
Esophagus. On opening pericardium a fusiform mass is recognized presenting on posterior wall. Pericardial surface smooth and movable over mass. No evidence of pressure on bronchi, though slightly adherent to both trunks; aorta free. On removal

of chest viscera the fusiform enlargement of esophagus is better seen. It begins 2.5 cm. above the cardia, and attains a maximum width of 4.5 cm. at a point 10 cm. higher. The esophagus was incised on its anterior surface. Four cm. above the cardiac is found an irregular polypoid mass made up of numerous bosses and extending in the axis of esophagus 9.5 cm. The point of attachment of lower end (pedicle), however, is 5.5 cm. from the cardia and extends upward 6 cm. This pedicle seems to be about 2.5 cm. in width; its accurate width cannot be determined without mutilation of the specimen. The new-growth is composed of bosses varying in size from 4 or 5 mm. in diameter to a larger mass 5 cm. in maximum diameter. (See illustration.) At the upper end is an ovoid almost free polypoid mass, 2.5 cm. by 1.5 cm., intensely congested and at one point shows beginning necrosis. The esophagus at the cardiac measures 4 cm. in circumference; 2 cm. above this point (hiatus esophagi) is a slight constriction measuring 3 cm. in circumference. Just over the mass the esophagus seems to be widest, measuring 9.5 cm. in circumference. Just above mass, 12 cm. from cardia, the esophagus measures 8 cm. in circumference, from which point it gradually narrows to what seems to be normal lumen (4 cm. in circumference) 22 cm. above cardia. The esophageal wall seems fairly thick but rather irregularly so, 0.25 cm. in thickness at the cardia, 0.4 cm. thick just over tumor, 0.2 cm. in thickness at the upper end.

Stomach is contracted, particularly at the pyloric end, contains a small quantity of grumous material. Mucosa intensely hyperemic, at points almost necrotic. These changes most marked in the pyloric area. Summits of the rugæ pointed and slightly eroded. Mucosa obscured by superimposed mucosa.

Intestine. One hundred and eighty centimeters above the ileocecal valve is a bifid Meckel diverticulum. It is 6 cm. in length, arises from free margin of intestine, has a diameter of 2 cm.: 2 cm. from its origin it divides into two small sacs resembling the letter "Y." Its mucosa is normal, overlying serosa is somewhat thickened, otherwise intestine is normal. Large arterial trunks show considerable atheroma.

With the exception of a marked arterial sclerosis there is no noteworthy lesion of other organs.



Squamous-cell carcinoma of the esophagus of the polypoid type. A, cardia of stomach. B to C, cardia of esophagus. C, Hiatus esophagi. D to E, area of maximum dilatation of the esophagus; from E upward the organ gradually diminishes in size. F, wall of esophagus. G to H, pedicle of tumor by which are attached the projecting bosses of the new-growth; at the base there appears to be but slight infiltration beneath the submucosa, although the esophageal wall is slightly thickened. The line F, G, H is near the midline posteriorly, from which the tumor has arisen.

Histologic examination of properly prepared sections shows that the growth is a typical epidermoid cancer, a squamous-cell epithelioma with marked keratinization of the cell nests and a richly cellular stroma. A tumor possessing such a structure must be of very low order of malignancy, resembling in its architecture the least malignant of the labial epitheliomas.

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April 14, 1904.

Eight Cases of Aneurysm of the Innominate Artery.

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Six of the following eight cases were collected from an analysis of 3309 autopsy records from the Philadelphia Hospital during eleven years (from 1892 to 1903, inclusive), covering Volumes VI. to XVI. of these records. Of the two remaining cases, one was

obtained from the Pennsylvania Hospital, through Dr. W. T. Longcope, and the other from the Episcopal Hospital, through Dr. William E. Robertson. To both of these gentlemen the writer desires to express his thanks and his appreciation of their kindness. This series forms the basis of a clinical paper dealing with the symptoms and physical signs of innominate aneurysm, to be presented to the Section on Medicine of the American Medical Association, in June, 1904; and to its *Transactions* the reader is referred for a complete consideration of the subject from an analysis of a series of 146 cases collected from the literature.

Philadelphia Hospital Cases.

It is unfortunate that in studying these cases the clinical notes are so inadequate. In four instances out of the six the presence of aneurysm was suspected; but in no instance was the diagnosis of innominate aneurysm made. Those portions of the autopsy record in each case that concerned the aneurysm or the condition of the heart and vessels have been given in full. The clinical histories have, as a rule, been given in full; being, even then, in most of the cases too sketchy and incomplete to furnish much of a clinical picture. The course of the case from day to day is not noted; and the simple entry "died" gives no clue as to the manner of death. In most of the cases, as attested by the autopsy notes, it was by rupture of the aneurysm.

Case I. Rosie D. Postmortem record 176, Vol. VIII. Pathologic diagnosis: Innominate aneurysm.

The patient was a colored female, aged forty-six years. The innominate artery, about an inch beyond the orifice, was the seat of an aneurysmal dilatation the size of an orange, containing laminated clot, and adherent to the clavicle, the first rib, and the upper part of the sternum. From it came off a diminutive subclavian; aorta showed atheroma.

Clinical Notes. Diagnosis: Aneurysm of the subclavian artery. Colored female, aged forty-six years. Patient is a well-developed and well-nourished woman. She shows marked dyspnea. The eyes are bulging, and the face has a restless, frightened expression. She states that about three months ago she discovered a "lump" in her neck, and had an attack of asthma.

Since that time the attacks have been growing more frequent and more severe. They are so bad now that she begs to have an operation performed on her neck.

In the neck there is a moderate-sized tumor, extending more to the right side, not moving when the patient swallows, and having an expansile pulsation with a thrill, but over which no bruit is heard. The tumor is not tender to palpation. There is no tracheal tugging. The tumor is fixed below. There is no heart-lesion demonstrable, but the heart's action is very forcible. The limbs are slightly edematous; the lungs and abdomen, negative.

Case II. John C. Postmortem record 299, Vol. XIII. Pathologic diagnosis: Innominate aneurysm. White male, aged forty-three years.

The aorta is thickened and roughened, showing patches of calcareous infiltration. Four centimeters above the aortic cusps the circumference is 18 cm. The ascending and transverse portions are widely dilated, as is also the orifice of the innominate. Just beneath its point of bifurcation there is a saccular dilatation extending inward in front of the trachea and reaching upward to the base of the cricoid cartilage. It contains a mass of laminated clot.

The heart-length from base to apex is 20 cm.; from right border to apex, 17 cm. The apex is in the seventh interspace, 3 cm. beyond the midclavicular line. The right auricle is distended with clot; the left is somewhat dilated. The left ventricular wall is 1.5 cm.; the right, 1 cm. The muscle is pale and friable, and there is nodular thickening of the mitral leaflets. The mitral valves are incompetent to the water-test, as are also the aortic valves. There is slight thickening, with retraction of the aortic cusps. Behind the left anterior cusp is a saccular dilatation about 3.5 cm. in diameter. The upper and exterior portion is very soft and pliable, and contains adherent clot and fibrin. The dilatation seems to proceed into the wall of the heart. The pulmonary and tricuspid valves are normal.

Clinical Notes. Diagnosis: Valvular heart disease.

White male, aged forty-three years. Chief complaint: cough, expectoration, dyspnea, epigastric tenderness, and distention of the abdomen.

On admission: Middle-aged man, well nourished. Pulses unequal; left much fuller than right. Temporal vessels prominent. The respirations are rapid and labored. There is impaired expansion of the lower left base, anteriorly and laterally; compensatory expansion of the right chest; fulness of the left lower chest anteriorly and laterally. The epigastric pulsation is strong, and there is a steady diffuse cardiac impulse.

Heart. No distinct apex-beat. Impulse reaches down in the anterior axillary line, almost to the eighth rib. The impulse is unequal and coarse, suggesting a friction. No impulse at base. Strong suprasternal pulsation. No diastolic shock. At apex a distinct systolic murmur, not transmitted to scapula. Over the entire remaining cardiac region, a distinct see-saw, friction-like sound is heard, obscuring the valvular second sounds. On percussion, the area of cardiac dulness is widely extended, reaching from the junction of the left third rib with the sternum, far out above the nipple, to the midaxillary line, and downward, to be continuous with the splenic dulness. The dulness reaches somewhat to the right of the sternum. There is a systolic murmur in the cardiac vessels.

March 4th. There is strong suprasternal pulsation; heavy epigastric pulsation. The heart-sounds as noted above. The murmurs heard replace entirely the normal sounds, and are endocardial in character. The pulse is full; Corrigan in type. Dyspnea marked; and cardiac impulse feeble and fluttering. Cheyne-Stokes breathing, and scanty urine. Death, March 7th.

Case III. John G. Postmortem record, 81, Vol. VI. Clinical diagnosis: Aneurysm.

Colored male, aged thirty-two years, unmarried, laborer. Clinical history not obtainable.

Mode of death, rupture of the aneurysm into the pericardium.

One-half inch below the innominate there is a calcareous patch, situated at the bottom of an aneurysmal dilatation, the innominate coming off from the uppermost border of the aneurysm, which is of the size of a pigeon's egg. In the ascending portion of the aorta, a quarter to one inch above the free margin of the aortic valves, is a dissecting aneurysm the size of a goose's egg—dissecting toward the left side posteriorly and beneath the pulmonary

artery. The aneurysm has ruptured just below the attachment of the pericardium, on its upper surface, between the right side and the right side of the pulmonary artery. The size of the orifice admits an ordinary small probe; and a small, irregular flap projects inward into the pericardium. There are several other smaller dissecting aneurysms which would probably have ruptured sooner or later. There are evidences of syphilis in other organs.

Case IV. Postmortem record, 285, Vol. IX. Colored male, aged fifty-one years. Pathologic diagnosis: Innominate aneurysm.

Right side of heart enormously distended with antemortem clots. Left auricle and ventricle contain postmortem clots. Tricuspid valve transmits five fingers and thumb. There is a saccular aneurysm of the aorta from the sinus of Valsalva to the beginning of the descending aorta, involving the innominate and the subclavian, which come off from the aorta as funnel-shaped dilatations. The wall of the aneurysm shows universal atheroma with fatty and calcareous plates.

Clinical Notes. Colored male, aged fifty-one years. Diagnosis: Valvular heart disease.

Large, well-nourished colored man, with eyelids somewhat swollen; legs exceedingly edematous; pulse weak, but regular.

Area of cardiac dulness enlarged, impulse diffuse and heaving, with a systolic thrill. At apex two murmurs, presystolic and systolic; and at the base, two murmurs, the systolic transmitted into the vessels of the neck, and the diastolic conducted down the sternum. The breathing is Cheyne-Stokes in type. The heart-sounds are everywhere distant and muffled; and the precordial dulness is wide, making it probable that there is pericardial effusion.

Two days later: The pulsation of the heart is felt distinctly, and seen also, below the costal border, at the left of the middle line; probably right ventricular pulsation. The heart-dulness extends as above. The patient suffers greatly with dyspnea, orthopnea, and Cheyne-Stokes breathing. The feet are very edematous.

Case V. Patten H. Postmortem record 239, Vol. XV. Pathologic diagnosis: Innominate aneurysm.

Colored male, aged thirty-eight years. The aorta is the seat of marked sclerosis, an aneurysm the size of a large orange springs from the origin of the innominate and the arch of the aorta, on

opening is 15 mm. in diameter. The innominate is still pervious. This aneurysm begins in the upper portion of the arch, extending within 3¾ mm. of the common carotid. The left subclavian is obliterated by a firm clot. The origin of this vessel cannot be found, but there is a depressed scar. The aneurysm is adherent anteriorly and laterally to the clavicle, sternum, and left ribs, and is partly covered by pericardium. It is filled with laminated clot.

Clinical Notes. Diagnosis: Aneurysm. Colored male, aged thirty-eight years. Chief complaints: cough, expectoration, asthma, strong pulsation of bloodvessels, and pulsation in the supraclavicular fossa on the right side.

Had syphilis at fifteen years. Present trouble began one year ago, when he says he received a blow over the clavicle. Later, he noticed pulsation of the carotid artery. Three months later he began to have "asthma"; he has had four spells in this time. Has had cough, accompanied with pain, for two months.

Examination of chest: On right the clavicle shows an old fracture (sternal end), and expansile pulsation of carotid artery can be seen. No thrill. The swelling is about the size of a pigeon's egg. On the right side of the chest, from the apex to the fourth rib and in the axilla there is a marked friction-rub.

The right temporal artery is not visible, the left prominent. The right facial and temporal are not palpable. The left facial and temporal are vigorous. The right external jugular is distended. There is a small tender nodule two inches above the clavicle. When this is pressed, pain is felt in the back of the neck and head. Both radial and brachial pulses are imperceptible. The sternal end of the right clavicle is prominent, and shows a distinct heaving pulsation, which can be felt at each side of the sternocleidomastoid muscle. There is no thrill, but a distinct double shock, the diastolic being the more powerful. There is no pulsation in either subclavian artery.

The aortic second is louder than the pulmonic second. Over the aneurysm there are two dull booming notes, the first prolonged and the second accentuated; over the left carotid there is a loud booming diastolic note.

There is slight impairment of the percussion over both apices. There is dulness under the sternal end of the right clavicle

The veins in the right side of the neck are more prominent than on the left. We notice a globular mass whose superficies is under the right sternoclavicular articulation, and which pulsates synchronously with the vessels of the neck. It exerts no traction on the trachea, and is dull on percussion half-way down the manubrium. The growth has a heaving pulsation and is very resistant.

Case VI. William S. Postmortem Record 229, Vol. XI. Colored male, aged forty-three years. Died from rupture of the aneurysm.

The innominate is but a band of tissue 0.25 cm. in thickness. The opening into the innominate is 1.75 cm. in diameter. It communicates with a cavity, lobular in form, 7.5 cm. in diameter, and obscured by a laminated clot. There are several external layers anteriorly which are evidently older. Within the external layer is a clot, irregularly globular, 4.5 cm. in diameter, within which is coiled the gold wire. The carotid and subclavian on the right are normal.

A saccular aneurysm arises from the anterior wall of the innominate artery; it projects forward and toward the median line, in front of the trachea, which is slightly flattened, but shows no erosion in its interior. The wall of the aneurysm is partly made up of the dilated artery. The arterial wall is a comparatively narrow strip, not exceeding 1.5 cm. from the aortic opening. Beyond this it is impossible to say whether the aneurysm is formed from the vascular wall or from inflammatory densely massed periarterial connective tissue. The weight of the mass—heart, larynx, trachea, and aneurysm—is 720 grams.

The cardiac cavities are empty, and the walls flabby. There are extensive adhesions inflammatory in origin. The larynx and all the great trunks of the neck are matted together. To demonstrate the relations it is necessary to secure the heart, the arch of the aorta, and the adjacent structures in one mass. The valves and orifices of the heart seem normal except for some old fenestra. The muscle is pale, soft, and pliable; there is abundant superficial fat. The coronary arteries show a moderate degree of atheroma, but this does not obstruct their lumen. The arch of the aorta is slightly dilated, and shows a few artheromatous patches. The right subclavian and the common carotid are normal.

Pennsylvania Hospital Case.

For permission to report which the writer is indebted to Dr. Longcope.

Frederick K. Autopsy record 130. White male, aged forty-eight years. Clinical diagnosis: Asthma.

On removing the heart, it is seen that the aorta is dilated just above the aortic valves. At the junction of the innominate and the aorta is a similar dilatation 7½ x 6 x 5 cm. From the extreme right upper portion of the sac arise the right carotid and subclavian arteries; and immediately to the left of the origin of this dilatation come off the left subclavian and carotid arteries, which are of unusual size. The aorta is immediately dilated at its arch, being approximately 6 cm. in circumference. The sac lies directly upon and is adherent to the trachea, and the cartilaginous rings are at this point softened. The sac reaches 1 cm. below the isthmus of the thyroid gland, and is attached to the pericardium as low down as the bifurcation of the trachea. On opening this dilatation the inner left portion of the sac, which represents the major portion, is found filled with a firm exudate and laminated clot, tightly adherent to the wall of the dilatation. The opening into the cavity is about 1 cm. in diameter.

Immediately above the aortic valve the aorta is much dilated, showing an open pouch on the right and left sides which is not clearly defined. The surface is markedly roughened and nodular, but there are no calcified plaques. There is general arteriosclerosis.

Clinical Notes. Hospital number 851. Diagnosis: Asthma.

White male, aged forty-eight years. Roofer. Born in Philadelphia.

Frederick K., aged forty-eight years. Cook. Admitted to service of Dr. Lewis, June 17, 1901. Measles as a child. Malaria eight years ago. Gonorrhea at twelve years of age. No other diseases. Been sick six weeks. Began with heavy cold, which developed into asthmatic attacks. Shortness of breath, bad cough and orthopnea.

On admission was very dyspneic and somewhat cyanosed. Wheezing asthmatic breathing, with profuse white expectoration.

Finger nails somewhat blue. Heart not enlarged, sounds entirely hidden by noisy respiration. Lungs resonant on percussion; breathing noisy: chest full of moist and asthmatic rales. Posterior resonance rather woodeny; no consolidation; asthmatic and moist rales at both bases. Frequent attacks of dyspnea. Death.

Pulse varied from 100 to 128. Respiration varied from 24 to 32. Temperature varied from 99° to 101⅘°.

Episcopal Hospital Case.

Kindness of Dr. Robertson. Pathologic diagnosis: Innominate aneurysm.

White male, aged thirty-nine years. There is a bulging of aorta in ascending portion of arch. The aneurysm, which involves the innominate artery alone, is about the size of a small orange. It occupies the entire extent of the artery, arising from its origin. The left common carotid and left subclavian come off in close juxtaposition to the neck of the aneurysmal sac. The right common carotid and subclavian come off from the upper and posterior aspect of the sac, and are of normal size and length. Firmly adherent to the posterior wall of the sac within was a laminated clot, while a more recent clot occupied the centre of the aneurysm.

The heart was not enlarged to any appreciable extent, though it was somewhat dilated. The mitral orifice admitted three fingers, the tricuspid four.

The aneurysm was adherent to all surrounding parts. It compressed the trachea from within 3 cm. of bifurcation to within 2 cm. of cricoid cartilage. On tracheal side, perforation almost complete was evident. The wall of the sac was very thin, and was torn on removing sternum, to which it was adherent.

Clinical Notes. Ward History, Episcopal Hospital, No. 968. Written after the postmortem, as the man only lived twenty-four hours after admission to the hospital. The diagnosis of aneurysm either of the arch or the innominate artery had been made before death.

About seven months ago began to have shortness of breath on exertion, with pain in the chest, most marked over upper end of sternum, on right side. For two days before admission had not

been able to swallow solid food. For two weeks has had a severe cough, with copious expectoration of white mucus, occasionally blood-streaked. Had been treated for asthma. For past few days his face and neck have been swollen and somewhat congested, this being more marked on right side. During the paroxysmal attacks of severe dyspnea with which he suffers the swelling becomes more marked.

Physical Examination. Breathing is very loud and harsh, especially on inspiration, being audible for some distance from bed. Respiration is so noisy that the heart cannot be satisfactorily auscultated, though sounds are not normal. Percussion over chest is normal except over upper end of sternum and to the right wall. Over this point or area it causes pain. There is slight bulging here, but nothing like a distinct tumor.

There is always great dyspnea. At times he is orthopneic, becomes cyanosed, unable to speak, and drenched with sweat. These attacks last from two to three hours. Says he has had them for two weeks. Is helped by hypodermic injection of morphin and atropin, and by inhalations of amyl nitrite. Next morning he seemed more comfortable and breathed somewhat easier early in the day. Later it became more labored again, and he finally became cyanosed, and died, probably from asphyxiation, at 4.30 P. M.

May 12, 1904.

A Case of Postpneumonic Endocarditis.

D. L. EDSALL, M.D., AND W. E. ROBERTSON, M.D.

The case was an example of a condition of constantly increasing importance, namely, pneumococcic septicemia ; and was also an example of the occasional decisive importance of blood-cultures in diagnosis. The patient was a woman aged forty-nine years, admitted to the Episcopal Hospital on April 23, the seventh day of a frank attack of acute lobar pneumonia involving practically the whole of the right lung. There was no previous history of interest, and the patient had no heart-lesion.

On the tenth day there was a drop in temperature and some general improvement, which at first seemed to us an oncoming crisis, but the patient grew worse again within twenty-four hours, and the temperature rose. It remained high, though irregular, during the following ten days, at the end of which death occurred.

Throughout this period the lung was slowly resolving, but the patient was extremely toxic and very delirious. She presented absolutely no physical signs explanatory of her condition. A careful watch had been kept for cardiac involvement, meningitis, and arthritis in particular, but no sign of any focus of septicemia could be discovered. The heart presented normal signs, except for a moderate degree of dilatation and some weakness of its action. There were no murmurs, and the heart was not irregular. A blood-culture made by Dr. Ghriskey a week after the beginning of resolution showed a pure growth of pneumococcus.

At the postmortem examination the lung was found largely resolved, but still dense. There were several splenic infarcts, but otherwise the conditions were not noteworthy, except for the heart, which showed a moderate degree of dilatation and a fresh vegetative and ulcerative lesion on the auricular surface of the posterior mitral leaflet. This lesion was about 2 cm. in length by 1 cm. in width, and was situated closer to the attached than to the free edge. Cultures made at postmortem were negative.

Proceedings

of the

Pathological Society of Philadelphia.

SEPTEMBER, 1904. NEW SERIES, VOL. VII., NO. 7.

TABLE OF CONTENTS.

SCHAMBERG and GILDERSLEEVE, A Bacteriologic Study of the Throats of One Hundred Cases of Scarlet Fever, with Remarks on the Relation of Bacteria to the Disease.—FUNKE, The Carotid Body: Anatomy, Histology, Embryology, and Tumors Arising from it.—MÜLLER, Accessory Pancreas in Posterior Wall of Stomach.—ALBURGER, Aberrant Pancreas in Wall of Jejunum.—WIEDER and SPRINGER, Clinical and Pathologic Reports of (1) Tuberculous Meningitis with Congenital Stricture of the Rectum, and (2) Uremia with Pericarditis.

A Bacteriologic Study of the Throats of One Hundred Cases of Scarlet Fever, with Remarks on the Relation of Bacteria to the Disease.

JAY F. SCHAMBERG, M.D.,

AND

NATHANIEL GILDERSLEEVE, M.D.

Numerous investigators have attempted within the past quarter of a century to discover the specific agent concerned in the production of scarlet fever. That the disease is produced by a contagium vivum, and that every case receives its infection from a pre-existing one, are propositions which command general acquiescence.

Plenciz,[1] of Vienna, as early as 1762 attributed the cause of scarlatina to living corpuscles. Hallier,[2] in 1869, found in the blood a micrococcus which he regarded as the specific agent concerned in the production of the disease. Hoffman,[3] in 1870, discovered in the sweat of scarlet-fever patients an organism corresponding to that of Hallier.

In 1872 Coze and Feltz[4] found in the blood a bacterium six microns long which was pathogenic for guinea-pigs. In the same year Riess[5] claimed to have demonstrated certain organisms in the blood, but failed to obtain results from inoculation or attempts

at cultivation. In 1875[6] Klebs found in the substance of an inguinal gland of a patient suffering from scarlet fever a spherical body made up of micrococci which changed their form; this organism he called "Monas scarlatinosum."

Tschamer[7] claimed that scarlet fever was caused by a cryptogam, which he named "Verticillium candelabrum," which is found in rotten wood; this he regarded as one stage in the development of the micrococcus found by him in the blood cells, scales, and urine.

In 1882 Eklund[8] found bodies in the urine of scarlet-fever patients which he called "Plax scindens;" he found similar organisms in the soil, in water, and on mouldy walls, and said that children living in the vicinity of such excavated soil contracted the disease.

Octerlony[9] observed these same bodies in the blood and urine of scarlet-fever patients.

In 1885 Pohl-Pincus[10] found cocci in the epidermic scales and also on the soft palate in cases of the disease. Klamann[11] made similar observations the same year.

In 1885 Fraenkel and Freudenberg[12] isolated a streptococcus from the internal organs in three fatal cases. Babes[13] found streptococci in 18 out of 20 fatal cases.

In 1884 Loeffler[14] isolated streptococci from the throats of patients suffering from this disease.

Power[15] reported a severe epidemic of scarlet fever which began among the patrons of a certain dairy where the cows were found suffering from a peculiar disease. Klein[16] investigated the circumstances of the epidemic, and isolated diplococci and streptococci. Klein,[17] in studying the blood of scarlet-fever patients, obtained an organism like the one isolated from the cows. He regarded this as the cause of the disease, and called it Streptococcus scarlatinæ.

Klein's conclusions were attacked by several investigators. Crookshank[18] saw an analogous epidemic among cows from which no scarlet fever was spread. He recognized the disease as cow-pox, and contended that the streptococcus isolated by Klein was the ordinary Streptococcus pyogenes. Kurth[19] found an organism resembling that of Klein almost constantly in the throats of scarlet-fever patients; this he named "Streptococcus conglomeratus." Gordon[20] later identified this organism with that of Klein,

who admitted the identity, and looked upon it as the cause of the disease.

Pearce[21] found streptococci alone and associated with other organisms in scarlet fever, in abscessed ears, in the antrum of Highmore, in bronchopneumonia, serofibrinous pleurisy, empyema, acute mitral endocarditis, cervical lymphadenitis, embolic abscesses in the lungs and kidneys, acute pericarditis, acute diphtheritic endometritis, etc., following the disease. In 11 cases of general infection the streptococcus was found in 9.

Booker[23] found streptococci in all cases examined (23).

In 1893, Fiessinger,[23] after a series of studies, announced his belief that the streptococcus was the cause of the disease. Dowson,[24] in the same year, expressed the opinion that scarlet fever was due to the streptococcus, and that the tonsil was the seat of the primary infection. This assumption was later championed by Bergé,[25] and by Lemoine,[26] who in a study of the throat in 117 cases of scarlet fever found the streptococcus alone in 23 cases, and present with other bacteria in 14 other cases.

d'Espine[27] found streptococci in the throat and blood, and states that the organism may be the cause of the disease.

Baginski and Sommerfeld[28] in 1900 published the results of a large number of bacteriologic examinations in scarlet fever. In 411 cases of this disease streptococci were constantly found in the throat. In a later series of 290 cases streptococci were found in 285. In this group they were found alone 21 times; with staphylococci 222 times, with diplococci 25 times, and with diphtheria organisms in mixed cases 17 times. In 701 cases, therefore, streptococci were absent but 5 times. From their several papers one is led to conclude that they are of the opinion that the disease is due to the streptococcus.

Charlton[29] found streptococci in 65 out of 117 cases examined.

Weaver[30] found streptococci in the tonsils of 18 cases. He also made cultures from the skin of 15 cases, but found nothing of interest.

Czajkowski[31] isolated from the blood of scarlet fever patients a coccus which was probably a streptococcus.

Marie Raskin,[32] in 1889, failed to find streptococci in the blood of 64 cases, but in 31 complicated cases she found the organism

in the pus in the internal organs and occasionally in the blood. In a second communication[34] she states that she succeeded in isolating from the blood and organs an organism of irregular form and size, growing like streptococci on artificial media.

Wright,[34] in 11 fatal cases found streptococci infection in 4.

Slawyk,[35] in 98 fatal cases, found bacteria in the blood of 52; streptococci were found 39 times, streptococci and staphylococci, 6.

Seitz[36] made cultures from the blood of 12 cases, and found streptococci in 1, which later terminated fatally.

Hektoen[37] studied the disease bacteriologically in relation to streptococcemia, and concludes that streptococci are occasionally found in the blood of cases of scarlet fever that run a short, mild and uncomplicated clinical course; that they occur with relatively greater frequency in the more severe and protracted cases of scarlet fever, in which there may also develop local complications and clinical signs of general infection, such as joint inflammation, but even in the gravest cases of this kind spontaneous recovery may take place, and finally that streptococcemia may not be demonstrable in fatal cases.

The theory that scarlet fever is a streptococcus disease does not seem to receive any direct support from this work.

In 1887 Jamison and Edington[38] isolated from the scales and blood of scarlet-fever patients a bacillus which they regarded as the cause of the disease. This organism was quite uniformly found in the blood after the third day, and in the scales after three weeks. This organism was, however, later demonstrated in the scales of ordinary dermatitis by Brown.[39]

A committee of the Medico-Chirurgical Society of Edinburgh investigated the claims of Jamison and Edington, and were able to find the bacillus in but 3 of 10 cases of scarlet fever; of 9 blood cultures results were obtained in 4; cultures from scales were made and inoculation experiments without results.

Class,[40] in 1897, described a diplococcus sometimes appearing in short chains, which he found constantly in the pharynx in scarlatina. It was also found in the blood, but rarely after the first day of the disease. He claims that inoculations into white swine produced an affection closely resembling scarlet fever. Page[41] found a diplococcus resembling that of Class in 5 cases.

L. Pfeiffer,[42] in 1887, describes protozoa-like bodies in the blood of scarlet fever and vaccinia. The significance of these bodies was not explained.

Mallory[43] has recently described certain bodies found in the skin of scarlet-fever patients which he believes to be stages in the developmental cycle of a protozoon. He has proposed the name "Cyclaster scarlatinalis" for these bodies. These bodies are found only early in the disease.

Mallory's studies constitute an interesting and important contribution to our knowledge of the subject, but further research is necessary before anything definite can be stated in regard to the specific pathogenicity of the bodies described.

Some time ago we examined bacteriologically a series of cases of scarlet fever occurring at the Municipal Hospital. The cultures were made between the second and sixth day of the disease. The blood of 20 cases was examined and negative results obtained in all. Cultures were made from the throats of 100 cases, and the following organisms isolated:

Streptococcus in pure culture	5
Streptococcus and diplococcus (Class)	5
Streptococcus and pseudodiphtheria	2
Streptococcus and pseudodiphtheria chromogenic	1
Streptococcus and Sarcina lutea	3
Streptococcus and B. pyocyaneus	1
Streptococcus and Micrococcus tetragenes	1
Streptococcus and Micrococcus tetragenes and diplococcus (Class)	1
Streptococcus and yeast	1
Streptococcus and Sarcina auriantica	1
Streptococcus and B. of colon croup	1
Streptococcus and Staphylococcus albus	2
	— 24

Streptococcus and Staphylococcus aureus	38
Streptococcus and Staphylococcus aureus and diplococcus (Class)	8
Streptococcus and Staphylococcus aureus, albus and diplococcus (Class)	1
Streptococcus and Staphylococcus aureus and pseudodiphtheria	3
Streptococcus and Staphylococcus aureus and pseudodiphtheria chromogenic	1
Streptococcus and Staphylococcus aureus and Micrococcus tetragenes	5
Streptococcus and Staphylococcus aureus and Sarcina lutea	4
Streptococcus and Staphylococcus aureus and yeast	1
Streptococcus and Staphylococcus aureus and albus	1
Streptococcus and Staphylococcus aureus and B. proteus vulgaris	2
	— 64

Staphylococcus aureus and albus	1
Staphylococcus aureus and citreus	1
Staphylococcus aureus and Sarcina lutea	3
Staphylococcus aureus and Micrococcus tetragenes	1
Staphylococcus aureus and Micrococcus tetragenes and pseudodiphtheria	1
Staphylococcus aureus and Bacillus pyocyaneus	1
Staphylococcus aureus and Bacillus proteus vulgaris	1
Staphylococcus albus and chromogenic pseudodiphtheria	1
Diplococcus (Class) and Micrococcus tetragenes	1
Diplococcus (Class) and chromogenic pseudodiphtheria	1
	12
	100

To summarize:

Streptococcus was found in	88 cases.
Staphylococcus in	73 cases.
A diplococcus corresponding to that of Class in	17 cases.

The streptococci were as a rule of the ordinary type; in a number of cases the conglomerate form, consisting of markedly curved and twisted chains, was found. This form grows on the various media in the same manner as the ordinary streptococci, and does not differ from it in pathogenic properties, and we cannot accept the idea that it is a distinct form. We encountered these conglomerate streptococci in a number of cultures made from normal throats.

A number of the staphylococcus cultures isolated were tested as to their pathogenic properties. These varied to some extent in virulence, but as a rule killed rabbits and guinea-pigs in a short time.

Dr. Class kindly supplied us with cultures of his organisms: those isolated from our cases correspond with those furnished us. Our experience has been that while this organism appears as a large diplococcus when first isolated and cultivated on certain media, it decreases in size to about 0.6μ and appears as micrococci, occurring singly and in pairs with an occasional short chain, and reacts on the various media in a manner similar to the ordinary staphylococci.

No other organisms were isolated that could be looked upon as having anything to do with the disease.

Cultures were made from the throats of 100 supposedly normal persons, and from 82 per cent. of them streptococci were obtained. A number of them were tested and found to be as virulent as those from other sources. These cultures were taken from the throats

of university students who had not been, as far as known, exposed to infectious disease.

The almost constant presence of streptococci in throats of scarlet-fever patients and their activity in the production of such complications as otitis media, cervical abscess, and endocarditis, have led certain writers to affirm their belief in the streptococcal origin of scarlet fever. Dowson, Bergé, and Lemoine have in recent years particularly championed this view.

There can be no question as to the constancy with which streptococci are found in scarlet-fever throats and at autopsy in the various organs and tissues.

This would constitute a strong argument in favor of its specific pathogenicity in scarlet fever were it not for the frequency with which it is found in other infectious diseases and in normal throats. For instance, in smallpox it is scarcely less ubiquitous than in scarlatina.

It is commonly found in the late pustules of smallpox and in many of the cutaneous complications, such as boils, impetigo, abscesses, erysipelas, gangrene, etc. After death streptococci are found in the cutaneous lesions and internal organs in nearly all cases. There would appear to be in many cases an agonal or postmortem diffusion of streptococci throughout the tissues. In forty autopsies on smallpox patients made by Perkins and Pay,[44] streptococci were found distributed throughout the body in 38. Ewing found streptococci in about 90 per cent. of the skin lesions at autopsy; he also noted the presence of streptococci in the blood after death in every one of 29 cases examined.

It is evident from the above and other investigations that the streptococcus is almost constantly found in fatal cases of smallpox. While no one can seriously entertain the idea that its role in smallpox is causal, it is so uniformly present that some writers believe it bears a peculiar relationship to the disease, differing from most secondary infections.

Many writers regard the smallpox bacteremia as the most frequent cause of death in smallpox. Councilman[45] says: "As a result of the study of the disease both by culture of the lesions and organs and by microscopic examination of the tissues we are inclined to regard bacterial infection as a more important agent in

bringing about a fatal termination than the specific parasite . . . . The bacteria are chiefly streptococci."

Such a statement might be made with equal force in relation to scarlet fever.

Perkins and Pay, and likewise Councilman, suggest that the streptococci gain entrance to the circulation through the bronchial and pulmonary mucous membrane.

It would seem that the relationship of the streptococcus to scarlet fever and to smallpox is quite similar. It gives rise in both to numerous complications, and not infrequently leads to a fatal termination. The proof that it is not the cause of smallpox is easy of demonstration. The proposition that the streptococcus bears no etiologic relationship to scarlatina is more difficult to disprove.

It appears to us reasonable that in certain infectious diseases, such as scarlatina and smallpox, the resisting powers of the tissues are so weakened against the streptococcus that the organism invades the system and works its noxious effects.

Until the streptococcus found in scarlet fever is shown to possess properties which trenchantly distinguish it from other streptococci; and until this disease is experimentally produced by inoculation of a pure culture of such an organism, the belief in the causal relationship of the streptococcus to scarlet fever cannot be maintained.

Conclusions.

1. That streptococci and staphylococci are to be found in the throat in the vast majority of cases of scarlet fever. It is significant to note that streptococci are present in a very large percentage of apparently healthy throats.

2. That both organisms are undoubtedly frequently concerned in the complications of the disease, but are not to be looked upon as the specific agents.

3. The diplococcus described by Class as the cause of the disease was found by us in but a comparatively small percentage of cases. We cannot regard this organism as bearing any etiologic relationship to the disease.

4. The interesting findings of Mallory of protozoa-like bodies

in the skin of scarlet-fever patients will doubtless stimulate research along these lines. It is quite possible that the failure in the past to discover the contagium vivum of the disease has been due to the fact that almost exclusive search for vegetable parasites has been made.

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May 26, 1904.

The Carotid Body: Anatomy, Histology, Embryology, and Tumors Arising from It.

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Histology and Anatomy.

The first intimation as to the existence of this organ was in all probability given us by Haller,[1] who, in 1743, wrote of the "de vera intercostalis origine," and again, in 1744, in "de nervorum in

arterias imperio." Neubauer,[2] in 1772, clearly refers to such a body in his "descriptio nervorum cardiacorum." Andersch[3] gave us a practical description of the organ in 1751, although his work is recorded in "tract-anatomico-physiologico," 1797. After that date the body was overlooked by many distinguished anatomists until 1833, when Mayer[4] recognized that besides two or three cervical ganglions there are other small ganglions in the neck which had been found and described by several authors, and which are more or less intimately associated with the sympathetic nervous system. Another ganglion of more importance, and according to his knowledge not previously described, was the structure now called the carotid body, which he located in the angle formed by the bifurcation of the carotid. It is the size of a grain of rice, oval in shape, red, firm, and vascular. In structure and consistency it resembles the superior cervical ganglion. By means of a small band it is attached to the carotid at the bifurcation. The body is in relation with the "nervis mollibus," formed by a plexus from the superior cervical ganglion; a branch from the glossopharyngeal nerve, after sending a branch to the "nervis mollibus," penetrates the ganglion; before entering the ganglion, however, it receives another branch from the vagus. In order to find the ganglion one need only remove the common carotid together with about an inch of the internal and external carotids. Mayer found the ganglion in horses and in calves in the bifurcation of the common carotid: in calves the relation between the ganglion and the "nervis mollibus" is greater than in the human being. Mayer says the ganglion intercaroticum in its relation, its form, and its texture may be likened to the celiac axis.

In the same year Valentine[5] described the body as pear-shaped, the apex of the pear pointing downward; it is gray in color and firm in consistency, and difficult to free from the surrounding structures. After maceration the internal structure is composed of reddish-white fibers, bands or septums which are interlaced and held together by fibrous tissue. The greater the angle of the carotid bifurcation, the more superficial the organ. Maceration in water, continued for several days, dissociates its capsule and makes clear its interlacing structure and the ganglionic character of the organ. Valentine believed the carotid ganglion received the com-

municating branches from the vagus. Branches are given off from both sides of the gland, part of which go to the artery, and the other part unites with the "nervis mollibus," so the gland is completely encircled with nerves. The band uniting the carotid body to the carotid artery, by microscopic examination, is found to be made up of nerve fibers.

Luschka,[6] in 1862, gives us the first microscopic description. He says the carotid body is not a ganglion in the ordinary sense of the term, but that it is a gland-like appendage or part of the sympathetic structure of the neck. It is surrounded by adipose tissue and a sheath from the adventitia of the carotid, which must be cut before the gland becomes visible. It is connected with the common carotid by means of a band of elastic tissue which becomes lost in the tunica media of the artery. The gland is firm and elastic; if compressed between two glass plates and examined with a lens, it is found to be composed of large and small spaces bordered by thick walls; the external portions of the walls are associated with fine connective-tissue substance containing many oblong cells. He divides the spaces in two types, one vesicular, the other tubular. The tubules can be traced some distance; their course is usually very irregular, and they lie between the vesicles. The vesicles and tubules contain round, granular, clear, and nucleated cells. Occasionally the cells in the vesicles resemble cylindric epithelium. He did not find any cells clearly ciliated, although some resemblance to ciliation could be detected. The arrangement of the cells in the vesicles and in the tubules is irregular; some, however, simulate the arrangement of the epithelium. The stroma of the organ contains many cells like those in the vesicles, either isolated or grouped. The organ, he says, receives its blood supply from the common carotid by means of a single branch, which divides and subdivides; the branches penetrate the organ and become lost in the stroma. He has never been able to find a capillary network.

Between the internal and external carotid, Luschka finds a twirl of nerves, which he calls the intercarotid plexus, and which, he says, is made up of fibers from the superior laryngeal, the glossopharyngeal, and a number of branches from the superior cervical sympathetic ganglion. He believes the purpose of this plexus is

to unite the sympathetic and the cerebrospinal nerves. So far as his observations go, the fibers from the superior cervical ganglion to the carotid plexus are related to the carotid gland; they also pass to the external carotid and its branches, as rami vasomotorii. In the substance of the carotid gland the nerves break up into a network which penetrates the vesicles and tubules of the gland. Polar ganglion cells, related to the nerve fibers, are rarely found, but apolar cells, either in groups or isolated, are abundant: at times they are enclosed within the membranes of the vesicles and tubules. Those which Luschka believes are nerve cells always remain posterior to that part he designates the glandular portion of the organ.

J. Arnold[7] in 1865 takes the ground that Luschka's description of the organ is incorrect and that it does not contain gland structure. He says the carotid body is supplied by four vessels derived either from the common or external carotid arteries, upon each of which hangs sometimes an oval and at other times a round lobe composed of three or four lobules depending upon the division of the main artery. The vessels forming the lobules of the glomeruli possess thin, circular, muscle layers. The epithelium seen in the average artery has reached a high degree of development. The efferent arteries soon after leaving the glomeruli surround the lobules and, in association with the network of corresponding glomeruli, form a widely meshed network. In noninjected preparations the apparent tubules are filled with finely granular nucleated cells; in the injected preparations they are occupied by gelatin. Fibers from the vagus, glossopharyngeal and the sympathetic form a plexus at the division of the common carotid between the branches; many fibers from this plexus penetrate the capsule of the organ. The fibers after reaching the inner portion of the body surround the lobes and lobules in a network. The gland, vesicles, and tubules of Luschka are identical with the divisions of Arnold's glomeruli. The occlusion of the tubules with epithelial masses is apparent only. The ganglion cells in proportion to the presence of the nerves are not so abundant. Apolar ganglion cells surrounded by a common capsule in which are also epithelial-like cells are not present.

Switzer[8] is convinced of the ganglionic character of the carotid

body. Sertoli[9] found a fibrous band surrounding the body described by Luschka, but regarded it as formed of bloodvessels. Pfortner[10] accepts Arnold's view; he recognized the tubules and acini as being formed from bloodvessels, the isolated bodies as glomeruli, and says the sizes of the latter vary; sometimes they are composed of few, other times of many vessels. He often observed several vessels merged into the wider one, which he held to be a vein. He found many nerves, no ganglion cells, but fat in the stroma.

Kölliker[11] merely refers to the work of Luschka and Arnold upon the carotid body. Eberth[12] believes the carotid body, like the gland of Luschka, is composed of whirls of vessels, which are mainly capillaries; some are normal, others widened. Frey[13] thinks the tissue of the carotid body is largely vessels; the cells present he likens to the cell elements seen in the adrenal or to Waldeyer's plasma cells.

Heppner[14] says this body varies in size from that of a hempseed to a cucumber seed; it is situated for the most part behind and in the median line of the common carotid, its apex projecting a short distance beyond the bifurcation. The organ is composed of a stroma and gland structure. The peripheral stroma is a continuation of the band connecting it to the carotid artery, in which band are many elastic fibers. From his preparations he is unable to decide whether to regard the lobules as cross-sections of vessels, as held by Arnold, or glandular, as maintained by Luschka, since, in peripheral lobules, he can recognize structures in the alveoli that may be regarded as a membrane; he inclines to the latter.

Marchand[15] finds in an embryo of four months the carotid body composed of a loose connective tissue, in which are many vessels and nerves. In the periphery the cells and fibers are arranged concentrically. At points the spheric groups of cells (zellballen) break up and gradually merge into a delicate fibrous tissue. In other places the cells form columns which very often show an inner relation to the vessels. Careful examination of the spheric groups of cells reveals lumina bounded by fine lines and filled with red blood cells. In the adult body two elements share in the construction of the lobules, namely, cells and vessels which are closely related to each other. In the connective tissue are col-

lections of cells, the largest of which are sharply circumscribed, at times by a delicate band of fibrous tissue. These groups simulate gland acini, but they possess a fine intercellular reticulum. The collections of cells either embrace the capillaries or are in contact with one side.

Paltauf[16] says the lobules are composed of many vessels that are surrounded by a narrow band of fibrous tissue upon which is situated a stratified layer of oval nuclei. In chromeosmic hardened preparation he recognized the vesicles, especially those limited with homogeneous walls and in which are the oval nuclei, as bloodvessels. He demonstrated muscle-fiber nuclei in their walls. According to his investigations, the carotid body is not composed of whirls of vessels only, but the winding vessels that form the lobules and correspond to the glomeruli are surrounded by a reticulum of delicate fibrous tissue, in the meshes of which are cells, some of these lining the vessel. He is inclined to retain the name glandula carotica in the same sense as we speak of lymph glands and thymus gland.

Kopfstein,[17] in an article on tumors of the carotid body, expresses the conviction that the normal organ is composed of vessels and cells. It presents lobulated structures, and is surrounded by a capsule. The cells are found between the vessels, and simulate in structure an acinus. These cell collections are intimately associated with the vessels. They are either concentrically arranged around the vessels or are closely united to one of their sides. Anatomically the body appears to be connected with the sympathetic system, since nerve fibers from the cervical ganglion enter it.

Princeteau[18] believes that according to the researches of Riefflel, it is not an intercarotid but a retrocarotid corpuscle attached to the carotid by a fibroelastic ligament called the ligament of Mayer. He says its position varies at times; in three cases he found it above the bifurcation, and in one case on the posterior surface of the internal carotid. The arrangement of the bloodvessels has struck Princeteau as being very curious; the arteries supplying the body break up in small tufts, each of which is made up of five small arteries. The main artery runs from below upward, one branch of which passes downward to reach the inferior pole. In

the body the ramifications of the arteries can be followed for some distance. He has found usually four or five nerves that depart from the superior pole, run parallel to one another, and enter the intercarotid space, where they intermingle with numerous nerve fibers to form the intercarotid plexus. The nerves are very numerous and emanate from various sources. In some cases he has seen them spring from intercarotid plexus, but in the greater number of instances they came from the carotid body. Summing up its structure, he concludes that the inferior pole is arterial and ligamentous and the superior pole venous and nervous.

Kohn[19] says that between the two carotids and above the bifurcation lies an organ peculiar to itself, which he designates "Paraganglion Intercaroticum." The cells, the nerve fibers and the ganglion cells are derivatives of the sympathetic system. The specific elements of the organ are the chromaffin cells, which spring from the sympathetic (embryonic) cells. Their cell substance is very well preserved by the chrome salts, but with other fixing agents preservation is poor; with chrome salts they stain yellowish. The ganglion is abundantly traversed with nerve fibers in which lie the spheric groups of cells and the ganglion cells of the intercarotid nerve plexus. The organ is richly vascular, but the vessels present nothing peculiar in their arrangement nor in their construction. Kohn says this body is neither glandular, as held by Luschka, nor is it glomerular, as maintained by Arnold; it belongs to a category of its own.

Heinleth[20] thinks the carotid body has a lobulated architecture. The structure of the lobules is composed of vessels and cells which bear a close relationship to one another. The lobules have the appearance of vesicular spaces, some of which are round, others tubular; they are either empty or contain granules, they possess limiting walls which at times are thick, containing many nuclei. The large spaces have laminated walls possessing muscle fibers. The small, more loosely built lobules show between the vesicular spaces many round apertures lying in a reticulated connective-tissue substance in which are round and oval nuclei.

Usually a nucleus lies along the periphery of each aperture; at times one lies in each lumen. The cells of the apertures contain an abundance of granular protoplasm; they are either low col-

umnar or polygonal, and simulate epithelial cells. The nuclei are often eccentrically placed. The apertures have no relationship to the reticular structure, except that they lie in contact with it. By injection the cells in the apertures are particularly conspicuous: they appear to line parts of the vessels and parts of the apertures in the reticulated structure. Reclus[29] says there is present more than simple vascular glomeruli; between the vascular meshes are cells which have an intimate relation with the vessels. Szymonowicz and MacCallum[30] think the carotid body is divided by connective-tissue septums into follicles which are filled with masses of small round cells, the so-called "zellballen." These cells resemble epithelium; they are either round or polyhedral, and seem to be closely associated with the bloodvessels. They are apparently of connective origin. These authors say the true nature of the body is unknown, but in all probability it is largely true reticulum. A branch of the carotid artery enters the body, breaks up into many smaller branches, one supplying each follicle. The branch of the follicle breaks into a capillary network, which unites with a vein at the periphery of the follicle. The body contains many medullated and nonmedullated nerve fibers, fine branches of which go to the follicles. Ganglionic cells are rarely found.

Boehm and Davidoff[31] say septums, derivatives of the capsule, divide the carotid body into lobules which are in turn again divided into small, round masses, "the cell balls," are composed of cellular cords, the elements of which are extremely sensitive to reagents. The cells are round or irregularly polygonal, and separated from one another by a delicate reticulum of connective tissue. The capillaries come in direct contact with the spheric groups of cells. The organ is comparatively rich in nerve fibers and contains a few ganglion cells.

Author's Study.

From the investigations I have made it is not possible to believe that the carotid body is present as often as is generally maintained. Of the eight fetuses examined, it was present only once. Three cats, one guinea-pig, and one rabbit contained no such structure. In one fetus a cervical ganglion occupied the position of the car-

otid body, and it was only after careful microscopic examination that the nature of the structure was recognized.

The body was found in the one instance attached to the common carotid artery 6 mm. below the bifurcation on one side, and on the other side it was found lying on the inner aspect of the external carotid, 0.5 cm. above the bifurcation. The attachment in both seemed to be by means of a delicate pedicle. They measured 7 mm. in diameter, were firm in consistency, and grayish-pink in color.

The body is enclosed by a fibrous capsule, the density of which varies at different points. From the capsule a band of fibrous tissue penetrates the body, separating it into two nearly equal parts; from this main partition others diverge toward the capsule, and separate the halves into lobules. The fibrous tissue appears from a tinctorial point of view to be of two types; the coarser fibers, with Mallory's reticulum stain, take the anilin-blue with intensity, while the more delicate strands select the acid fuchsin in a somewhat modified hue—a deep lilac. With Van Gieson the delicate fibers fail to stain, or select the acid fuchsin very faintly.

The fibrous tissue contains many bloodvessels. Many of these present nothing unusual, while others are lined with cells having large round or oval eccentric nuclei that evince no greater staining affinity. The cell nucleus reacts to Mallory's reticulum stain in a manner similar to the delicate fibrous reticulum. The protoplasm is not abundant and possesses, with Mallory's reticulum stain, a reaction somewhat similar to that of the nuclei. Every now and then the entire bloodvessel wall is made up of somewhat similar cells. These cells are found, not only in and about the bloodvessel wall, but are also distributed throughout the dense fibrous tissue, especially the lobes already mentioned.

The lobules are composed of collections of cells that have no definite arrangement. In instances they appear separated by a delicate reticulum. In only a few does their disposition simulate gland structure. They are very closely set, making it difficult to outline the individual cells. The cells are large, their protoplasm is abundant; the nuclei are large, as a rule oval, and, like the protoplasm, react poorly to stains. Minute bloodvessels can be found in all parts of these lobules. In most instances their walls are

barely perceptible, but they are, nevertheless, nearly always present. Every now and then one is found that apparently penetrates a large cell, but even then a delicate wall can be made out. There appears to be an intimate relation between these cells and the bloodvessels; just how they are related I cannot from my present studies say. I am strongly of the opinion that these lobules are produced by the proliferation of the endothelial cells of the bloodvessels. The encroaching cells give rise to the apparent delicate wall observed. The sections examined contained neither multipolar cells nor nerve fibers.

Embryology of the Carotid Body.

Luschka believes the carotid body develops from the endoderm. In an embryo of fourteen weeks Valentine found the carotid gland present on both sides; its shape, firmness, and connecting filaments were the same as in the fully developed organ.

Stieda,[21] in embryos of 11 mm., found a round body no longer connected with the epithelium of the pharynx nor of the thymus, and regards it as the interglandula caroticum. Katschenko[22] says the structure from which Stieda believes the carotid body develops corresponds to the so-called Katschenko's thymus ganglion. He finds an ellipsoidal body on the internal carotid, at the bifurcation, in embryos of 14 mm. and 18 mm. The thickening adventitia is pushed to one side and later toward the bifurcation; at the same time many vessels arising from the internal carotid enter the body. Fischelis,[23] on the other hand, regards the glandula caroticum as originating from the tissue lying between the approximating ectodermal and the endodermal layers and does not consider the organ as developing from epithelial structure. Pierre de Neuron[24] believes the carotid body develops from the third branchial cleft. In sheep, the organ referred to is found near and above the bifurcation of the carotid, although in embryos of 18 mm. it is not separated from the thymus. Rabl,[25] in mammifera and in birds, found the endoderm of the third cleft furnished the ventral diverticulum for the thymus and the dorsal bud for the intercarotid. Paltauf concurs in the view expressed by Katschenko.

Van Bemmelen,[26] in snakes, saw the retrocarotid corpuscle develop at the expense of the endoderm of the third cleft. Pren-

nant,[27] after studying the opinions already given, concluded that the retrocarotid gland develops in the form of an epithelial bud at the expense of the endoderm of the third branchial cleft. Princeteau, from its position and relation to the common carotid, looks upon the origin as being in common with that of the common carotid which develops from the third branchial arch. Borst[28] says the carotid body originates from the mesenchyme. Heinleth believes the first indication of its development is a cellular thickening of the primitive carotid at its posterior and outer periphery. Kohn thinks the carotid body develops from the embryonal ganglion cells of the intercarotid plexus.

Tumors of the Carotid Body.

CASE.*—F. J. R., aged forty-eight years, mechanic. Six years ago the patient first observed a growth just below the angle of the inferior maxilla and in the anterolateral part of the neck. It grew slowly but apparently continuously; it did not inconvenience him in the slightest degree. During these six years he has gained in weight.

Examination reveals a tumor that extends from the angle of the right inferior maxilla, 2 cm. below the upper border of the larynx, along the anterior border of the sternomastoid muscle. The outline of the tumor is indefinite to inspection; from its most elevated portion, which is 5 cm. to the right of the median line on a level with the superior border of the larynx, it merges gradually into the surrounding structure; upon palpation, however, the outlines of the growth are definite; it is firm, about 7 cm. by 4 cm. in diameter, and not attached to the skin; it is freely movable from side to side, but not vertically. There was present neither pulsation nor expansion; the pupils were equal and the face was not flushed.

At the operation, which was performed by Professor Hearn at the Jefferson Hospital, the growth was found firmly attached to the common, internal, and external carotid arteries and internal jugular vein. Bleeding from the tumor was profuse. In attempting to dissect the neoplasm from the vessels the jugular vein and the

* For the use of the clinical notes in this case I am indebted to Professor Hearn, of the Jefferson Medical College, who operated upon the patient.

external and internal carotid arteries were torn; this accident necessitated the ligation of the common carotid below, the internal and external carotid above, and the internal jugular vein above and below the growth in order to complete its removal.

For several days after the operation the patient could not speak above a whisper. He gained strength slowly, but left the hospital eight days after the operation. In a short time he began to complain of headache, especially in the median parietal region; then it was noticed that he became irrational for short periods only; there were no other symptoms to indicate a tumor of the brain. Soon after leaving the hospital he began to lose flesh rapidly; he complained of fatigue. There was no evidence of recurrence at the original site of the tumor nor at any other point. He died of cerebral anemia nine weeks after leaving the hospital.

Microscopic Examination of the Tumor. The specimen consists of an irregular mass measuring 5 cm. by 3 cm. by 3 cm. It is dark red, soft, and encapsulated. The capsule for the most part is smooth and glistening. The specimen cuts with ease; the incised surfaces are dark red, granular, and contain many small cavities filled with blood.

The tissue was fixed in Bensley's fluid, embedded in paraffin, sectioned and the sections stained with hematoxylin and eosin by Van Gieson's method, for elastica by Weigert's method, with Mallory's reticulum stain, with iron hematoxylin, for myelin sheaths by Weigert's methods, and for ganglion cells by Nissl's method.

Histology. The sections present an alveolar arrangement. The capsule is comparatively thick, composed of dense, wavy, fibrous tissue, and contains a few lymphoid cells. From the capsule, bands of fibrous tissue penetrate the tumor, giving support to the structure and, by division, form alveoli of a fairly uniform size separated by this stroma-like tissue; the fibrous septums thus formed are fairly constant in thickness and structure, although at points the fibrils are coarsely grouped, and in not a few areas they are the seat of a hyaline degeneration. The alveoli are occupied by cells that are oval and round and measure from 15 to 20μ in diameter. The nuclei are large, round or oval, and stain with a moderate degree of intensity; the oval nuclei stain deeper than

the round. The protoplasm is abundant, granular, and reacts to its selective stain with a fair degree of intensity. In some alveoli the cellular contents are closely packed, the cell outline indistinct and the grouping irregular; in others the cells are less crowded, and there is a suggestion of tubular arrangement. In a few alveoli there are besides these cells a number of erythrocytes. Only now and then can an intercellular reticulum be demonstrated. The walls of the alveoli are thin, and in many instances vessels appear to course in them, most often in the center of the wall, but every now and then vessels are seen lying very close to the alveoli, being separated from them by delicate strands of tissue only. There is no difficulty in demonstrating red blood cells in these vessels.

Elastica was found in the bloodvessels only. Nerve fibers were not found, and ganglion cells were also absent. The bloodvessels are large and abundant in the supporting structure of the tumor, and are filled with blood.

Diagnosis. Since in many places the bloodvessels can be seen in the alveolar walls and at times separated from the alveolar contents by a delicate strand of tissue, the supposition that the tumor cells are derivatives of perithelium is entirely reasonable. I am, therefore, favorably impressed with the term "perithelioma."

Etiology. These tumors occur especially in adolescence and in adult life. In the cases reported the youngest patient was 18 and the oldest 60. Neither sex seems predisposed; in the collated cases there were eight females and six males; in one of the reported cases the sex is not given. In two cases there was a history of malignant disease in the family. One of the tumors was first noticed after the extraction of a tooth and fracture of the inferior maxilla; this patient had a history of inflammation of the throat and glandular swelling. In another patient there was a history of tonsillitis. One of the tumors was first observed after confinement. Heinleth explains the formation of these tumors as follows: The carotid body develops until the age of puberty, when it either atrophies or arrests in development; if the body continues to grow a tumor is formed.

TABLE GIVING ATTAINABLE DATA CONCERNING ALL THE REPORTED TUMORS OF THE CAROTID BODY.

No.	Operator.	Name, sex and age.	Duration of disease.	Symptoms.	External relations and appearances.	Ligations.	Nerves injured.	Microscopic appearance.	Clinical diagnosis.	Pathologic diagnosis.	Results.	References.
1	Riegner, 1880	..... F. 32	1½ yrs.	Visible pulsation; no inequality of pupils; no flushing of face; expansion not noted; size of hen's egg.	No metastasis adherent to vagus; internal jugular and sympathetic	All carotids; pharyngeal; internal jugular.	Vagus and sympathetic.	Alveolar structure, each alveolus bounded by a structure that contains a capillary; alveolus has cells.	Lymphoma	Whether of endothelial or perithelial origin Marchand does not say, but is malignant.	Died of bronchopneumonia	Reported by Marchand, Festschrf f. Virchow, 1891, Bd. i.
2	Maydl, published in 1886	..... M. 28	6 mos.	Evident pulsation; no expansion; size of pigeon's egg.	No metastasis; hard, encapsulated in bifurcation.	All carotids; pharyngeal; superior thyroid.	.....	Periphery is alveolar; alveoli contain polygonal cells; center more fibrous tissue and pigment.	Lymphoma	Paltauf says perithelioma of carotid gland.	Postoperative hemiplegia and aphasia; in four years no return.	Allg. Wien. med. Zeitsch., 1886; Paltauf, Ziegler's Beiträge, 1892, Bd. xi.
3	Dittel,	Ph. S. M. 32	Several months	Pulsation slight; skin movable over tumor; last week's growth rapid; size of hen's egg.	Encapsulated, hard, vascular, lobulated; near it small tumor; carotid adventitia infiltrated.	All carotids; internal jugular vein.	.....	In periphery columns and cylinders of cells, blood; spaces lined by endothelium; center fibrous, contains few cells.	Not made.	Same as above.	Died of secondary hemorrhage.	Paltauf, Ziegler's Beiträge, 1892, Bd. xi.
4	Gersuny, 1886	..... F. 18	Not noted.	Not recorded; size of hen's egg.	Encapsulated; uneven, gray, granular; on section many canals; 3 cm. below mastoid.	All carotids; pharyngeal.	Paralysis of the left vocal cord.	Cell cylinders conspicuous; degenerated blood and cells in the alveoli; pearl-like in alveoli; like endothelioma.	Tuberculous lymph node.	Same as above.	Paralysis of left vocal cord; no return in four years.	Ibid.
5	Albert, 1891	..... M. 35	5 yrs.	Pure blood on tapping; no expansion; last year rapid growth; size of an apple.	In bifurcation; encapsulated, dark red, vascular, lobulated; recurrence in one year.	External carotid.	.....	Similar to the last, but presents hyaline degeneration.	Not made.	Same as above.	Cured; removed again one year later.	Ibid.

6	Maydl, 1893	J. R. F. 46	16 yrs.	Visible pulsation; murmur over tumor; no expansion; painful recently; size of hen's egg.	Adherent to jugular; carotid's media infiltrated; metastasis; encapsulated, hard, vascular.	All carotids; pharyngeal.	Sympathetic.	Stroma and alveoli, oval cell in the alveoli, numerous bloodvessels; hyaline degeneration of stroma and alveolar walls.	Carotid tumor.	Endothelioma.	Cured; mydriasis marked but stationary.	Kopfstein, Wien, klin. Rundschau, 1895, Bd. ix.
7	Maydl, 1895	..... M. 34	4 yrs.	Pulsation ceases upon compressing carotid; systolic murmur; recently it inconveniences.	Enlarged lymph node near tumor; carotid wall not infiltrated.	Common, internal, external carotids; pharyngeal; superior thyroid.	Vagus, sympathetic, hypoglossus, facial.	Same as No. 6; structure of lymph-node like tumor proper.	By exclusion intercarotid tumor.	Malignant; does not state definitely; says similar to No. 6.	Cured; aphonia, paralysis of left vocal cord.	Ibid.
8	Heinleth, 1900	..... M. 60	.....	Noticed after extraction of a tooth; site in the bifurcation of common carotid.	Tumor encapsulated and lobulated.	Tumor removed without any ligations.	None.	Cell groups enclosed by fibrous bands; between groups are capillaries with thin walls; tumor cells derived from capillaries.	.....	Peritheli-oma of the carotid gland.	Cured.	Heinleth, Centralblatt f. Anat., 1900, Bd. ix.
9	Malmoosky, 1899	..... F.	10 yrs.	Skin free; fremitus over tumor pulsation; bruit, synchronous pulse in temporals; growth rapid in last year.	Surface smooth.	Common, external, internal carotids; intern. jugular.	Removed 8 cm. of pneumogastric.	What were first thought to be lymph spaces are bloodvessels; cell proliferation from external portion of the wall.	Lympho-sarcoma of the carotid sheath.	Peritheli-oma of the carotid gland.	Cured.	Malmoosky, Review, 1899, Contrib. a l'etude des tumeurs de la gland carotid.
10	Simouschine 1901	..... F.	8 yrs.	Growth slow; recently pain in ear; skin free; tumor soft, movable sidewise, size of walnut.	.....	Common, internal, external carotids; intern. jugular.	None.	Eccentric development; cannot tell whether cells are derivatives of endothelium or perithelium.	Fibrolipoma.	Cannot say whether endothelial or perithelial.	Cured.	Seance, 401, de la Soc. de Chir. de Moscow, 1901.
11	Reclus and Chevassu, 1903	..... F. 49	5 yrs.	Pulsation; no expansion; souffle; upon pressure tumor apparently disappears; soft, 4 x 5 cm.	Encapsulated, brown, smooth, lobulated, elastic, adherent to the large vessels and nerves.	... .	Cervical and branch of facial.	Masses of cells surrounded by capillaries whose walls are thin; the cell nuclei project into their lumina.	Tumor of the retrocarotid corpuscle.	Peritheli-oma of the retrocarotid corpuscle.	Cured.	Review de Chir., 1903, No. 8, vol. xxviii.

No	Operator.	Name, sex and age.	Duration of disease.	Symptoms.	External relations and appearances.	Ligations.	Nerves injured.	Microscopic appearance.	Clinical diagnosis.	Pathologic diagnosis.	Results.	References.
12	Scudder, 1903	..... F. Betw'n 20 & 30	9 yrs.	Size of pigeon's egg; movable sidewise and over skin; pulsation; no expansion.	Tumor attached to the carotid artery.	Common, internal, external carotids.	.....	Many vessels, between which are large round and spindle cells and originate in tissue between vessels.	Not noted	Variety of angiosarcoma known as perithelioma of carotid gland.	Cured in thirteen months; no recurrence.	Scudder, Amer. Jour. of Med. Sci., Sept., 1903.
13	Macphater,[1] 1903	..... F. 34	6 yrs.	First noticed after confinement; growth slow until recently, then pain and uneasiness; pulsation; no expansion; left side.	Firm, nodular, invaded the surrounding structure; vascular.	Common, external, and internal carotids; internal jugular.	None.	No description.	Not noted.	Undetermined.	Cured.	New York and Philadelphia Med. Journ., 1903, vol. lxxviii. No. 4.
14	MM. Cuneo and Francois Dainville 1903	 23	3 yrs.	Right side lancinating pain radiating into right ear; myosis right eye, vasomotor disturbance of face, swallowing difficult.	Not adherent, posterior to carotid; compression of sympathetic and pneumogastric slightly.	None.	None.	Fibroma presenting large vascular and lymphatic cavities.	Not noted.	Tumor of retrocarotid corpuscle.	Cured.	Société anatomique, July 10, 1903.
15	Hearn, 1903	T. J. R. M. 48	6 yrs.	Right side below angle of jaw; growth slow; no inconvenience, no pulsation, not attached to skin.	Encapsulated, firm, adherent to surrounding structure, carotids on its anterior surface.	Common, external, and internal carotids; internal jugular.	None.	See text.	Question of fibroma, lymphoma, or aberrant thyroid.	Perithelioma of the carotid body.	Cured of the operation, but died two months later.	

[1] This case was not reported as a tumor of the carotid body, but the clinical history, general characters, and the operative difficulties seem to me to establish clearly the nature of the growth.

These tumors have been mistaken for tuberculous lymph nodes, lipoma, fibrolipoma, lymphosarcoma, aneurysm, and aberrant thyroid; upon superficial examination cystomas of the neck may be mistaken for tumors of the carotid body.

Although Borst and Reclus say these tumors are benign, Marchand and Kopfstein state definitely that the tumors in their cases were malignant. Paltauf notes the recurrence of the tumor in one of his patients a year later. While I am inclined to look upon these tumors as malignant, I believe that in the case reported in this article the patient died of cerebral anemia rather than as a result of the neoplasm itself.

See table of reported cases, page 222.

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April 14, 1904.

Accessory Pancreas in Posterior Wall of Stomach.

By GEO. P. MÜLLER, M.D.

(From the Pathologic Institute of the German Hospital.)

I am indebted to Dr. A. O. J. Kelly for permission to report the following:

A Japanese, male, aged thirty-four years. Death from tuberculosis.

At Autopsy. Miliary tuberculosis of lungs, liver, spleen, and kidney; areas of circumscribed arteriosclerosis of the aorta with atheromatous ulcer of the thoracic aorta; tubercular ulceration of intestine; tubercular mesenteric, bronchial, and mediastinal lymph nodes; accessory pancreas in wall of stomach.

The accessory pancreas was observed 8 cm. from the pylorus as an oval nodule 1.5 x 1 cm. in size, firm, flattened, and projecting from below the mucosa, and slightly upon the peritoneal surface. Upon section the nodule is observed to be composed of gland-like tissue.

Microscopically the accessory body is found in greater part to occupy the submucosa, but many lobules have separated the muscle bundles. The glandular tissue is identical with that of the pancreas, and contains numerous islands of Langerhans, smaller in size than those of the normal gland. In the connective-tissue septa between the lobules are numerous small ducts, lined with columnar epithelium, sometimes dilated, and in several instances surrounded by a ring of connective tissue. The circular muscle bundles are much distorted by the infiltration of numerous lobules of pancreatic tissue, but are not atrophied from pressure.

The pancreas proper showed some round-cell infiltration, and connective tissue increase in the interlobular septa, but was otherwise normal.

Aberrant Pancreas in Wall of Jejunum.

HENRY R. ALBURGER, M.D.

In the course of the pathologic service of the Philadelphia Hospital the body of an adult white male was submitted for post-mortem examination with a clinical history of chronic pulmonary tuberculosis, together with multiple lipomata. During the autopsy tuberculosis of the lungs, bronchial and mesenteric lymphatics and intestines was found, following the usual type of lesions, and in the upper jejunum a few centimeters below its junction with the duodenum, close to two characteristic tuberculous ulcers, was found a solid, white area, somewhat elevated as a nodule above the mucous surface, which at the time was supposed to be a large, solitary, tuberculous nodule, not yet ulcerated. This area was roughly circular in outline, about 1 cm. in diameter, and raised as a rounded elevation about 4 mm. above the adjacent mucous surface. The tissue was firm on pressure and intimately attached to the deeper coats of the intestinal wall; the mucous membrane over it intact, the color of the nodule pinkish and without any marked inflammatory areola, and on section the substance was seen to be fairly firm and of a whitish color. Throughout the remainder of the intestinal tract numerous characteristic tuberculous ulcers were encountered.

The results of close gross inspection being unsatisfactory for the first hypothesis (*i. e.*, that the nodule was tuberculous in character), the structure was reserved for microscopic examination.

Minute observation has indicated that the mass is composed of pancreatic tissue in the form of a circumscribed nodule lying between the mucous and muscular layers of the intestinal wall. The overlying mucosa is somewhat thin but comparatively normal, except at the apex of the nodule, where it is very thin and the cells have lost their staining reactions, showing necrosis, probably post-mortem in nature. From this position at the apex of the nodule many ducts may be traced into the more deeply placed glandular structure, indicating this as the point of escape of the secretion of the gland.

The bulk of the mass is made up of pancreatic tissue in much

the same condition and relations as seen in the normal pancreas, with the exception of a distinct increase in the connective tissue throughout; the bands of interlobular tissue being very thick and dense and sending prolongations into the lobules, thus breaking them up into smaller and unequal divisions. The cells of the parenchyma are also somewhat smaller than those seen in the normal pancreas. The bodies of Langerhans are extremely difficult of recognition, if they are present at all; in some of the acini are groups of cells which suggest them, but are not sufficiently characteristic to be clearly demonstrable. Two of the larger ducts lying between the pancreatic tissue and the apex of the nodule are greatly distended and cystic, and in one there is a suggestion of a papillomatous ingrowth of the surrounding connective tissue; this cystic condition is probably due to obstruction of the ducts by bands of connective tissue so much in excess in the nodule. Throughout the parenchyma, especially in and adjacent to the connective tissue about the bloodvessels and the interlobular trabecule, we find many small collections of small round cells with scanty protoplasm and deeply stained nucleus, showing the presence of some inflammatory changes in the organ.

From the position of the pancreatic tissue and its condition and the situation of the ducts we may assume that we have a functionating aberrant or accessory pancreas in the wall of the upper jejunum.

Discussion.

Dr. Robertson said that four years ago he had found a nodule of pancreatic tissue in the wall of the ileum.

Dr. Longcope had found an ectopic pancreas only once in five hundred and sixty autopsies at the Pennsylvania Hospital. It was situated in the jejunum below the duodenum, and was of the size of an almond.

Dr. Coplin said that one form of malformation of the pancreas had not been mentioned, viz.: pancreas multilobulare, shaped like that of the cat. He was skeptical as to the occurrence of ectopic masses in the duodenum, as the pancreas is frequently found edged over by the duodenum. He had not recognized an accessory pancreas in over three thousand autopsies.

Dr. Willson quoted Opie, who had found implantations of pancreatic tissue in the duct of Wirsung, and less rarely in the smaller duct (Santorini), and in the papilla of Vater.

Dr. Riesman said that while he had not seen cases of ectopic pancreas, he had, several years previously, shown to the Society a specimen of accessory spleen contained in the tail of the pancreas. The little spleen had been studded with miliary tubercles.

Dr. Stengel said that he had received some microscopic sections supposed to be carcinoma of the duodenum, but had found them to represent an ectopic pancreatic nodule.

Dr. Müller, in closing the discussion, said that Opie had found ten instances in a series of eighteen hundred; at the German Hospital but one in between four hundred and five hundred autopsies had been found. *May* 12, 1904.

Clinical and Pathologic Reports of (1) Tuberculous Meningitis with Congenital Stricture of the Rectum, and (2) Uremia with Pericarditis.

HENRY S. WIEDER, M.D., and HAROLD L. SPRINGER, M.D.

(From the Clinical Laboratory of the Presbyterian Hospital.)

The following is a brief report of the clinical history and course of a case of tuberculous meningitis with congenital stricture of the rectum and a case of uremia with pericarditis.

The tuberculous meningitis occurred in a child four and one-half years of age. The family history contained a record of tuberculosis on her mother's side in three members of the family. Noteworthy in the child's previous history was the fact that she was obstinately constipated during the first six months of her life, never obtaining a bowel movement except by artificial means, and also the fact that her cervical glands were very much enlarged last winter.

The symptoms were more or less typical.

Four spinal punctures were performed, small amounts of a clear colorless fluid being obtained. After the first two punctures there was an apparent decrease in the severity of the symptoms.

Tubercle bacilli were not obtained from the spinal fluid. The leukocytes varied from 7000 to 42,000.

Necropsy Report. The dura was not adherent to the skull-cap. Upon opening the dura there was an escape of considerable cerebrospinal fluid. The pia of the base was thick and opaque, with some pus under it. Around the optic chiasm and the vessels about the circle of Willis were numerous small white bodies the size of mustard seeds and much resembling miliary tubercles. These were much more numerous along the Sylvian artery. The section of the brain showed nothing abnormal except dilatation of the ventricle from an excess of cerebrospinal fluid. There were no tubercles upon the choroid plexus.

In the anterior mediastinum, just under the first portion of the sternum, was a large softened lymph gland that on section contained a yellow, purulent, probably tuberculous fluid. The bronchial lymph glands were much enlarged, but the lung showed no evidence of tuberculosis. The heart was normal, except some cloudy swelling of its muscle. The liver, kidneys, pancreas, adrenals, and stomach were normal.

In the rectum, three inches from the anus, was a constriction in the bowel. The bowel appeared somewhat thickened, and the interior of the constricted portion was white and hard and marked by longitudinal striations. There was no dilatation of the bowel above this point.

Microscopic Report. The bronchial glands showed tuberculosis in the stage of caseation. One had gone on to pus formation.

A section was cut from the middle of the constricted portion of the rectum, the microscopic examination of which showed the mucous and submucous layers of the rectum were almost gone, a suggestion of mucous membrane being present; the muscular layer was entirely absent. A growth of fibrous tissue had taken the place of these normal coats, so that the section seemed one of fibrous tissue instead of intestinal wall.

The absence of inflammation of rectum, as evidenced by previous history and microscopic examination, and the history of obstinate constipation during the first six months of life, make it probable that the stricture was congenital. The fact that no further difficulty was experienced after the first six months may be

explained by compensatory hypertrophy of the bowel above the site of stricture.

The case of *uremia* and *pericarditis* occurred in a man fifty-five years of age, stationary engineer by occupation. In July, 1902, he had an attack of gout, starting in the great toe and travelling up the foot, which confined him to his bed for ten weeks, and from that time he commenced to decline in strength. He would have edema of the legs occasionally for a couple of weeks at a time, easily became dyspneic, passed urine frequently, and complained of vertigo. He had always been a heavy drinker.

Physical examination on admission: Gouty nose, puffed face; tongue dry, parched, with whitish fur upon it. Lungs negative, but for evidence of congestion. Heart enlarged considerably to the left, no murmur, but first sound lacks muscular tone. Liver extends from sixth rib to two fingers' breadth below the costal margin.

Blood. Hemoglobin, 45 per cent.; red blood corpuscles, 2,020,000; leukocytes, 7000.

A couple of days after admission patient developed pain over precordium, and a coarse, rasping, superficial friction rub was heard in the fifth interspace to the left of the sternum. His temperature rose from 97° to 101° on May 19, 1903, and remained up for a few days. He became nervous and restless and could not sleep. He was obstinately constipated. His urine once showed a trace of albumin, and on another occasion was negative, and at no time were there any casts found in a sedimented specimen, although we have since learned that they were found prior to his admission. The amount of urine was between 64 and 72 fluidounces. Before death he had a convulsion.

Necropsy Report. There was no fluid in the abdomen. The relations of the abdominal viscera were normal. There were 18 fluidounces of a clear yellow fluid in each pleural cavity, and no pleural adhesions except at the right apex. In the apex of the right lung were several old scars, apparently the result of tuberculosis. The bronchial glands were not enlarged.

There was considerable inflammation around the pericardium, which contained 2 ounces of a clear yellow fluid. The heart was nearly covered by the left lung, which was adherent to the pericardium by fresh adhesions. The epicardium and the parietal

layer of the pericardium were generally adherent from deposits of a fresh fibrin which covered a large portion of the heart. The fibrin was particularly marked around the great vessels.

Heart. The left ventricle measured 25 mm. in thickness, was somewhat friable and yellow, and showed spots of fibrous tissue. The mitral valves were somewhat puckered, and the chordæ were thick and apparently short. The aortic valve showed a marked degree of atheroma. The three edges of the tricuspid valve were white and puckered, but the orifices of the valve were not obstructed. The right ventricle and the right auricle were considerably dilated, and the right ventricle measured 8 mm. in thickness. Weight of the heart, 1100 grams.

The intestines, adrenals, and pancreas were normal. The liver was somewhat fatty and pale, but not enlarged. The stomach showed a moderate degree of hypertrophic gastritis. Both kidneys were small and very much scarred, especially the left one. The capsules were adherent, and there were numerous small cysts upon the cortex and on section. The cortex was very much contracted. Weight of right kidney, 120 grams. Weight of left kidney, 90 grams.

Pathologic Diagnosis. Hypertrophy and dilatation of the heart, with atheroma of the mitral and tricuspid valves. Acute pericarditis. Fatty and contracted kidneys. Fatty liver.

Microscopic Report. Kidneys. The epithelial cells of the tubules are granular and in some places detached. Many glomeruli are replaced by fibrous tissue, and the capsules of Bowman are quite thickened. Cysts are scattered throughout the section, varying in size, and the entire organ shows a marked degree of chronic passive congestion.

The liver also shows this chronic passive congestion to a marked degree, and in places fatty degeneration has begun.

June 11, 1903.

Proceedings
of the
Pathological Society of Philadelphia.

November, 1904. New Series, Vol. VII., No. 8.

TABLE OF CONTENTS.

McCarthy, Cholesteatoma Vasculosa of the Choroid Plexus of the Lateral Cerebral Ventricles.—Ellis, Specimen from a Case of Rhinophyma.—Coplin and Ellis, Trypanosoma Diseases.—Sailer, Carcinoma of the Stomach with Hyperacidity.—Stanton, Aneurysm of the Arch of the Aorta Mistaken Clinically for Pulmonary Tuberculosis.

Cholesteatoma Vasculosa of the Choroid Plexus of the Lateral Cerebral Ventricles.

D. J. McCARTHY, M. D.

(From the William Pepper Clinical Laboratory and the Laboratory of the State Live-stock Sanitary Board.)

The deposition of cholesterin crystals in nervous tissues undergoing various pathologic processes is well recognized by neuropathologists. The presence of cholesterin crystals in the choroid plexus is, however, a comparatively rare occurrence. I have yet to see a primary deposition in the choroid plexus of a human being. In the horse it is of not infrequent occurrence, and is always associated with some pathologic process in the parenchyma or interstitial tissue of the plexus.

A very interesting form of cholesterin formation in the choroid plexus is seen in the "cholesteatoma vasculosa telæ choroideæ et ventrilculorum cerebri" described by Kitt, *Pathologische Anatomie des Hausthiers*, vii. S. 581. The case coming under my observation gave rise to some difficulty on account of the peculiar structure and situation of the tumor mass. The horse presented nothing in the clinical picture to suggest a brain tumor other than a certain amount of stupidity and confusion—the so-called

"dummy." At the autopsy a body the size of an English walnut was found almost free in the left lateral ventricle. It was of a soft, almost fluid consistence in the center, surrounded by a tough, fibrous capsule, and attached by a small band of tissue to the choroid.

The microscopic appearance led at first to a diagnosis of endothelioma by the pathologist, on account of certain peculiarities in structure, but the appearance is typical of the cholesteatoma vasculosa.

The capsule is composed of fibrous tissue derived from the bloodvessels of the choroid, and in this case contained a large quantity of elastic fibers. In the meshes of the fibrous tissue large numbers of cells, the size of a polynuclear leukocyte but mononuclear in type, are seen. The nucleus is, however, irregular in shape, and not infrequently appears to be made up of several globular masses of chromatin. Irregular spindle cells with a pale, newly-formed nucleus are also present. As the center of the tumor is approached the reticulum of connective tissue becomes looser, giving much the appearance of lymphoid tissue. The greater part of the area of section is taken up by the accumulation of round cells. The majority of these are the size of a polynuclear leukocyte, but do not give the staining reaction of leukocytes. The nuclei are sometimes round, but more often of the same irregular type as is seen in the meshes of the capsule. The irregularity of the shape of nuclei is often very marked, but true polynuclear cells are not seen. A large round, mononuclear, vesicular type of cell is also seen. The nucleus is round or irregularly oval, and stains a pale blue with hæmatoxylin. A peculiar type of cell is seen here and there throughout the section. This is a multilocular cell, three to four times the size of a polynuclear leukocyte. The nucleus is small and eccentrically situated. The cell body is divided up by septa of chromatin, giving the appearance of a bee-hive arrangement. A type of cell similar to this, but not identical with it, is found as a normal structure in the Raynaud bodies in the peripheral nerves.

A large part of the area of section is taken up by the crystalline masses above described. These are more or less limited by capsules of connective tissue. In some areas the crystalline sub-

stance is the only substance present. In others, and these are the more numerous, rows of cells, some round, some spindle type, fit in the areas between the crystalline deposits. The nuclei of the spindle cells are large and pale; those of the round type of cell are very irregular. The arrangement of the cells in rows gives a picture at first glance not unlike that of an endothelioma.

The tumor tissue is everywhere richly supplied with blood-vessels. The presence of melanin pigment in considerable quantities is probably the result of previous hemorrhage. No recent hemorrhage was present in the sections examined.

It will be seen from a study of the picture (Fig. 1) that the structure of the tumor under consideration does not at all correspond to the cholesteatoma met with in the human being. In the latter the pearls are composed of flat, epithelial-like cells, whereas the structure of the choroidal tumor does not present any such appearance. The highly vascular connective-tissue network is filled with round cells, and the areas of cholesterin deposit is merely a sac-like compartment within the tumor mass, covered by connective tissue. Between the cholesterin crystals round cells of irregular nuclei, probably leukocytic in origin, are arranged in rows, giving the appearance of an endothelioma type of tumor.

The origin of this tumor mass is very obscure. It has been found in horses dying of glanders, and one explanation given is that of an infection of the ventricles and choroid by the organism causing this disease. But why a suppurative process within the ventricles should be so localized, without evidence of infection elsewhere in the brain, is not very clear. Proliferative change in the connective tissue of the choroid is not at all infrequent in other infections. It is seen in its most intense form in forage poisoning in cattle. To a less intense degree it is frequently met with in tuberculosis in the lower animals and the human being. It was present in the choroid plexus of a patient who died from acute internal hydrocephalus. That an irritating substance in the ventricular fluid, such as is present in forage poisoning, or a bacillary infection not going on to suppuration, but producing a nonpurulent inflammatory process, is a more likely explanation of the condition than a single infection such as glanders. The deposition of cholesterin is undoubtedly a secondary process, and may

FIG. 1.

Section of a central area of the tumor formation, showing the capsule of a cholesterin area, with rows of large cells arranged on columns through the center of it. Magnified 350 times.

FIG. 2.

Central area of tumor mass, showing the arrangement of the crystalline areas and round cell infiltration. Under a low power (Leitz ob. 3, oc. 4).

correspond in the lower-animal type to the calcified concentric bodies so frequently met with in the choroid plexus of the human being. A careful study of the choroid plexus some years ago, in an attempt to get some explanation for meningitis serosa in the human being, led me to the conclusion that little was to be gained from the literature or from autopsy findings in the choroid plexus of man. In the lower animals a much wider field is presented in the study of the physiology and pathology of this part of the brain which may have some bearing on the obscure conditions met with in clinical medicine.

Specimen from a Case of Rhinophyma.

A. G. ELLIS, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

The patient from whom this specimen was removed was a tailor by occupation. There was no history of trauma of the nose. Fifteen years ago he had an attack of what was probably acne rosacea, in which the nose and adjacent borders of the cheek were most prominently involved. This was followed by a nodular growth of the nose, involving all except the upper fourth of that organ. The growth was bluish-red in color, gave rise to no pain, and breathing was not interfered with; the projecting mass of tissue, however, caused serious annoyance to the patient while eating, and for this he sought relief.

Operation consisted in removal of the central portion of the growth by means of an elliptic incision and paring down of the part on each side that could not be thus included. Contrary to expectation, there was but little hemorrhage. The wound healed by first intention. The cosmetic result, as shown by the illustrations, is very satisfactory, quite normal-appearing skin having been reproduced over the areas that were reduced by paring.

The specimen received for examination consisted of several masses of tissue, the largest being 4 by 5 cm. in extent and 1.5 cm. thick. One surface was formed of wrinkled skin bearing numerous small, nodular elevations. The color was darker than that of normal skin, being of a slightly bluish tint; scattered over the

surface were many small, depressed, reddish areas that resembled punctate hemorrhages.

The histology of sections from this tissue is very simple. They are composed largely of fibrous tissue which, on one border, is marginated by stratified epithelium, such as is found in normal skin, though the layers are fewer in number than usual. The corium and subcutaneous tissue are directly continuous with and similar in structure to the deeper portions of the section, which are composed of a fairly loose, cellular fibrous tissue containing numerous lymph spaces and bloodvessels. The fibrils of this tissue are exceedingly wavy and irregularly placed. A very conspicuous feature of the sections is the sebaceous glands, which are greatly increased in size and in some areas apparently in number. Slight evidence of cystic change is shown by some of these glands, and in one instance the gland structure has almost entirely disappeared, the space being occupied by polynuclear leukocytes; there is, however, little or no evidence of inflammatory change in the surrounding tissue. Around certain of the hair follicles are quite dense accumulations of small mononuclear cells. The diagnosis given is soft fibroma of the skin with distention of the acini and possibly hyperplasia of the sebaceous glands.

The only recent reference to rhinophyma, an indefinite name that has been given to this condition of the nose, appears to be that of von Bruns,[1] who reports eleven cases, eight of which he operated upon. The condition is also spoken of as hypertrophy or elephantiasis of the nose; some writers consider it simply a late stage of acne rosacea, or a type of that disease they designate acne hypertrophica. Von Bruns believes acne rosacea and rhinophyma possess nothing in common; neither does he consider alcohol an etiologic factor in rhinophyma, which he attributes to the growth of congenital "anlage." The growth in his cases had persisted for from five to twenty years, the age of the patients ranging from fifty to sixty years. The apex and alæ of the nose are irregularly thickened; at times the affected portion is covered by lobulated projections that are usually sessile, but occasionally pedunculated. Deep grooves are sometimes present, dividing the growth into several, most often three, distinct lobes. In extreme cases the lobules hang over the upper lip and even upon the chin.

Fig. 1.

Fig. 2.

Rhinophyma. Appearance of patient before operation.

FIG. 3.

FIG. 4.

Rhinophyma. Appearance of patient after operation. The corrugated condition of the skin is more marked than on the nose itself.

Von Bruns describes the growth as being soft in consistency and possessing a glistening, fatty surface, from which can be expressed plugs of ribbon-like masses of sebaceum; the color usually is purplish or bluish-red, sometimes gray, occasionally unchanged. Histologically the growth is composed of vascular connective tissue and enlarged and cystic sebaceous glands filled with sebaceous material and epithelial detritus. Proliferation of epithelium is not present. The growth has been designated fibroma or cystadenofibroma, according as the fibrous tissue or cysts predominate. This essentially describes the present specimen except that cystic change is here almost entirely lacking.

The privilege of studying and presenting this specimen, the notes of the case, and the accompanying illustrations, I owe to Dr. W. W. Keen,[2] who has elsewhere reported the case in full.

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February 11, 1904.

Trypanosoma Diseases.

W. M. L. COPLIN, M.D., AND A. G. ELLIS, M.D.

Dr. Coplin and Dr. Ellis presented a communication on trypanosoma diseases. They briefly described the known forms of the parasite and exhibited specimens of the *Trypanosoma lewisi* in the blood and tissues of rats. Through the kindness of Dr. Kinyoun they were able to show the *Trypanosoma brucei* in the blood of a horse. They had inoculated a large number of white rats with blood containing the *Trypanosoma lewisi* obtained from Dr. Novy, of Ann Arbor. In three inoculated white rats the parasites could not be demonstrated in the blood after the forty-fifth day, and in one after the fifty-ninth day; in one gray rat (Blockley) the parasite was still present in the blood seventy days after coming under observation. Although several of the rats died, in none of them was there reason to believe that death had resulted from trypanosoma infection, with the possible exception of one in which, at autopsy, a beginning pneumonia of a catarrhal type was found. No cultures were made from this case, but bacteria could not be found in the sections. This was of interest, as in one of the

cases of reported human trypanosomiasis the patient had developed a pneumonia, from which, however, she recovered.

Control rats kept with the infected animals did not acquire the parasite. The urine from a dead inoculated white rat contained no trypanosomas, although the blood was full of them. Usually the parasites disappear from the blood postmortem, but in one case they were demonstrable thirty hours after death.

For the purpose of determining the frequency of infection, Dr. Coplin and Dr. Ellis had examined forty-three rats from the Philadelphia Hospital, and found twenty-five (58 per cent.) infected. Of seventeen rats caught in the Jefferson Medical College, nine (53 per cent.) contained parasites. Dr. Glenn, of Asheville, North Carolina, was kind enough to send sixteen barn rats; five (31 per cent.) of these were infected. Of 6 barn rats examined near Clarksburg, West Virginia, none were found to contain the parasite. The infection is much more common in young rats. In the Philadelphia Hospital series no full-grown rat was found infected. Of the rats caught at Jefferson, two evidently old animals contained the parasites. The authors have not found trypanosomas in the saliva of infected rats; and dead infected rats were frequently eaten by others, the latter not acquiring the infection. The parasites were not present in a number of fleas found on infected rats. A litter (six) of young rats born of an infected mother (inoculated white rat) contained no parasites. One of the observers has been bitten twice by infected rats without any untoward results. Five mice and a bat were examined, but no trypanosoma was found.

Carcinoma of the Stomach with Hyperacidity.

JOSEPH SAILER, M.D.

Cases of carcinoma of the stomach with persistent hyperacidity and a constant finding of free hydrochloric acid in the stomach contents have been frequently reported, but still form such a small proportion of all cases of gastric carcinoma, no matter where situated, that they possess a considerable degree of interest. The clinical history of the present case may be given very briefly.

A mulatto, aged forty-eight years, a cook by profession, was

brought to the hospital with a history that one month previous while eating fish the food was regurgitated without retching and without a bitter or sour taste. Since then it was almost impossible for him to retain food although he was constantly hungry and very thirsty. He lost altogether 40 pounds in this period. Stomach tubes and esophageal bougies were passed upon him, and it was found that there was a stricture apparently spasmodic in character, at the cardia, which could temporarily be relieved by the passsage of a large bougie. The esophageal sound could be obtained if the bougie were passed, but would disappear in a short time. The patient was able to take food and liquids, but as he continued to lose weight Dr. Roberts performed a gastroenterostomy on March 30th. The wall of the stomach appeared to be normal. From this time test meals were obtained about once a week through the gastric fistula, showing on one occasion a total acidity of 35; free hydrochloric acid was present but not estimated. On the second occasion the total acidity was 65, free hydrochloric acid 7, determined by Congo red, dimethylamidoazobenzol, and Günzberg's reagent. The patient left the hospital on the 23d of April because he was not allowed to eat all he wished. On the 26th he returned with the statement that he had indulged very heartily in food on the 24th and on the 25th had had severe pain and felt extremely prostrated. There was evidence of peritonitis and the patient died on the 28th of April.

The autopsy was performed by Dr. Randolph of the Polyclinic laboratories. He found an adenocarcinoma of the stomach and esophagus, metastasis to the small intestine, atrophy and pigmentation of the spleen, cirrhosis and pigmentation of the liver, and peritonitis. The stomach wall was greatly thickened in all its coats. It was pinkish white with red areas scattered in different portions. The specimen under the microscope showed all the coats were thickened, especially the submucous coat. There was considerable proliferation of connective tissue, forming alveoli and tubular spaces which were filled with atypical and fairly typical epithelial cells, the lymph spaces were also filled with these cells. In many places there were foci of degeneration. A similar area was found in the small intestine, but whether it was really a metastasis or an evidence of multiple primary infection it is hard to say.

The nature of this tumor appears to be reasonably clear. It corresponds histologically in all respects to the ordinary adenocarcinoma. The specimen of the stomach, however, was unfortunately not saved, but at the autopsy I was able to inspect it and the pyloric portion appeared to be normal. Most unfortunately portions of the pylorus were not saved for microscopic examination, so it is impossible to say whether the glands were histologically perfect or not. Sections from the cardiac end of the esophagus showed the presence of this peculiar infiltration. There was no evidence of metastasis to the mesenteric glands or to the liver. In a careful study of these sections I cannot entirely rid myself of the idea that possibly there was a primary sclerotic inflammatory condition of the wall of the stomach, and that the epithelial proliferation took place as a secondary process. It may be indeed that we have to do with an inflammatory process that was tuberculous in nature, although the section from the stomach wall and from the intestine, aside from small areas of necrosis did not give definite information on this point. A number of cases have, however, been described, of tuberculosis of the mucous membrane of the gastrointestinal tract associated with an epithelial proliferation that closely resembles, if it is not identical with, that of carcinoma. Why, at the time of operation, the stomach wall appeared to be normal, although at the time of the autopsy, four weeks later, it was greatly thickened and almost cartilaginous in consistency, it is impossible to determine. The operation wound was surrounded in all directions by the thickened tissue. Dr. Roberts and Dr. Fenellosa, the resident assisting him, are both positive upon that point, and the observation of myself and many others who saw the wall of the stomach clearly as it was pulled through the abdominal wound. are in entire accordance with their statements. It is of course not impossible that the tumor had commenced in the neighborhood of the cardia, and then after the operation grew very rapidly. Why, in view of this rapid growth, the patient's condition should have shown relative immediate improvement it is difficult to say.

Aneurysm of the Arch of the Aorta Mistaken Clinically for Pulmonary Tuberculosis.

WILLIAM B. STANTON, M.D.

The patient was a male, aged forty-four years, who had never had any serious illness until the present attack. He admitted gonorrhea, but denied syphilis. He had always used alcohol to excess. The family history was negative as far as tuberculosis was concerned.

The present illness began with hemoptysis in January, 1903, which was not excessive. He felt fairly well until June of the same year, when he became short of breath and began to lose in weight. These symptoms, together with cough and bloody expectoration, increased in severity until December 18, 1903, when he came under my care as a supposed consumptive.

Physical Examination. The man was well nourished, the face looking slightly swollen and cyanotic. The dyspnea was marked. The veins of the neck were large, especially upon the right side. Speaking was difficult, owing to the rapid breathing, and was interrupted by a frequent short cough. The expectoration was copious, almost plum-colored, and of thick, gelatinous consistency. The chest was well shaped, with no depressions above or below the clavicles. Around the costal margin there were numerous dilated venules and over the surface of the chest and abdomen there were many small angiomas. The motion of the chest was limited, but apparently equal upon the two sides. On the right side, below the third rib, the chest seemed more prominent, and in this locality an indistinct pulsation could be detected upon close examination under a good light. This was made difficult because of the rapid breathing, frequent cough, and the inability of the patient to hold his breath. The pulsation seemed to be most marked just below the nipple to the inside of the midclavicular line. On the left side there was distinct retraction (systolic), with dimpling over the precordia.

Palpation confirmed inspection and detected a third area of pulsation in the second left interspace about three fingers' breadth from the sternum. No thrills were noted over the pulsations.

Fremitus was absent over the area of pulsation on the right, otherwise apparently normal.

Over the right lung the percussion note was impaired under the right clavicle as far as the third rib, where it became perfectly flat, the flatness extending as far as the fifth rib. In the fifth interspace the note became a little clearer. Laterally the flat note extended to the midaxillary line. Posteriorly there was hyperresonance except at the base, where there was impairment. Over the left lung the percussion gave a fairly good note. The cardiac dulness ran into the dulness noted upon the right side, and above into the dulness over the area of pulsation in the second left interspace. The apex was in the midclavicular line in the sixth interspace.

Auscultation over the right lung anteriorly showed bronchial breathing and numerous moist rales as far as the third rib. Over the flat area very distant bronchial breathing (evidently transmitted) could be heard. The vocal resonance was increased below the clavicle, and over the dull area there was a distant pectoriloquy. Posteriorly numerous rales were heard, the expiration was prolonged, and the vocal resonance was increased. Over the left lung anteriorly the expiration was prolonged; there were a few dry rales. Over the heart a faint systolic murmur was heard at the apex, which became much louder over the pulsation in the second left interspace, where the second sound was markedly accentuated. A loud second sound could be heard over the pulsating area to the right, but no murmurs. The pulse was very weak in comparison to the laboring heart; it was regular and apparently equal on the two sides. The pupils were equal and no tracheal tug could be elicited. The voice was not hoarse. The abdomen showed no abnormality.

An examination of the sputum for tubercle bacilli gave a negative result. The temperature was normal.

The patient died about two weeks later and permission was given to open the thorax. Coming off from the first part of the arch of the aorta there was a large sac about five inches in diameter, which was so tightly adherent to the chest wall that it was torn in removing. From the distal portion of the transverse arch a second aneurysm about the size of a small lemon grew forward.

Throughout the larger part of its extent the pericardium was adherent to the heart muscle. All of the valves were competent. The right lung was compressed, but showed no macroscopic evidences of tuberculosis. No tuberculous lesions were found in the left lung.

The mistake in diagnosis can only be explained upon the supposition that the examinations had been carelessly made or that there had been a sudden increase in the size of the sacs.

INDEX.

Aberrant pancreas in wall of jejunum, 227
Accessory pancreas in posterior wall of stomach, 226
Acid-fast bacilli, 19
Actual and comparative resistance of acid-fast bacilli, 19
Alburger, Henry R., aberrant pancreas in wall of jejunum, 227
Anchylostoma, coagulation of blood in, 173
Anders, J. M., discussion on arteriosclerosis, 170
Aneurysm of arch of aorta mistaken clinically for pulmonary tuberculosis, 246
of innominate artery, 190
Anspach, B. M., exhibition of specimens, 1
Arteriosclerosis, early lesions of, 133
of gastrointestinal tract, 165
of nervous system, 156

Bacilli, acid-fast, 19
Bacteriologic study of throats of cases of scarlet fever, 201
Behrend, Moses, report of a case of brain tumor and of a case of ruptured tubal pregnancy, 29
Bladder, sarcoma of, 125
Brain tumor, 29

Cancer, etiology of, 82
Carcinoma of esophagus, 178
of stomach with hyperacidity, 243
Carotid body, 209
Carroll, J. F., exhibition of specimens, 2
Cholesteatoma vasculosa of the choroid plexus of the lateral cerebral ventricles, 233
Cirrhosis of liver, 44
Clark, J. G., exhibition of specimens, 1, 2
Coagulation of the blood in anchylostoma, 173
Coplin, W. M. L., carcinoma of the esophagus, 178
changes in the intercostal muscles and diaphragm in infective processes involving the lung and pleura, 65, 81
discussion on aberrant pancreas, 228
discussion on acid-fast bacilli, 54
discussion on sarcoma of the bladder and prostate glands, 130
discussion on the coagulation of the blood in anchylostoma, 177
early lesions of arteriosclerosis, with special reference to alterations in the elastica, 133
exhibition of specimens, 2, 3
trypanosoma diseases, 242
Craig, F. A., exhibition of specimens, 7
Cryer, M. H., exhibition of specimens, 3
Cysts of urachus, 125

Daland, Judson, discussion on arteriosclerosis, 171
discussion on a case of Filaria immitis in the heart of a dog, 96
exhibition of specimens, 3

Edsall, D. L., postpneumonic endocarditis, 199
Elastica, alterations in, 133
Ellis, A. G., exhibition of specimens, 2, 12
specimen from a case of rhinophyma, 238
trypanosoma diseases, 242
Endocarditis, postpneumonic, 199
Eshner, A. A., discussion on a case of xanthoma, 61
Esophagus, carcinoma of, 178
Exhibition meeting, fourth annual, 1

Farr, Clifford B., case of splenomegaly, with cirrhosis of the liver, 44
exhibition of specimens, 4
Filaria immitis in the heart of a dog, 91
Fourth annual exhibition meeting, 1
Francine, Albert P., aneurysm of the innominate artery, 190
Frazier, C. H., exhibition of specimens, 4
Funke, John, carotid body: anatomy, histology, embryology, and tumors arising from it, 209
exhibition of specimens, 2

Gastrointestinal tract, arteriosclerosis of, 165
Gildersleeve, Nathaniel, bacteriologic study of throats of cases of scarlet fever, 201
exhibition of specimens, 15
Goldberg, Dr., exhibition of specimens, 4

Hartzell, M. B., discussion on a case of xanthoma, 61
Hawke, W. W., discussion on acid-fast bacilli, 54
Hemiplegia, uremic, 62
Hemorrhage, pancreatic, 52
Howard, Frederic Hollis, case of Filaria immitis in the heart of a dog, 91

Innominate artery, aneurysm of, 190
Intercostal muscles and diaphragm, changes in, 65

Jejunum, wall of, aberrant pancreas in, 227

Landis, H. R. M., exhibition of specimens, 7
Levenson, R. S., exhibition of specimens, 7
Lipomatosis of pancreas, 88
Liver, cirrhosis of, 44
pathology of, 33
Loeb, L., discussion on the changes in the intercostal muscles and diaphragm, 81
presence of a substance inhibiting the coagulation of the blood in anchylostoma, 173, 177
Loeb, L., recent contributions to the etiology of cancer, 82
Longcope, W. T., arteriosclerosis of the gastrointestinal tract, 165
discussion on aberrant pancreas, 228
exhibition of specimens, 7
Lung and pleura, inflammations of, 65

McCarthy, D. J., cholesteatoma vasculosa of the choroid plexus of the lateral cerebral ventricles, 233
discussion on arteriosclerosis, 172
exhibition of specimens, 8
McConnell, G. exhibition of specimens, 9, 11
sarcoma of bladder and prostate gland causing a cyst of the urachus and bilateral hydronephrosis in a nine-month-old baby, 125
McFarland, Joseph, case of xanthoma, 56, 61
discussion on a case of Filaria immitis in the heart of a dog, 96
discussion on acid-fast bacilli, 29
exhibition of specimens, 9
MacKinney, W. H., exhibition of specimens, 10
Morbid growth, report of committee on, concerning Dr. Stahl's specimen, 55
Müller, Geo. P., accessory pancreas in posterior wall of stomach, 226, 229
exhibition of specimens, 4, 10
pancreatic lithiasis with atrophy and lipomatosis of the pancreas, associated with pulmonary tuberculosis, 88

Nervous system, arteriosclerosis of, 133
Norris, C. C., exhibition of specimens, 2

Pancreas, lipomatosis of, 88
Pancreatic hemorrhage, 52
lithiasis, 88
Postpneumonic endocarditis, 199
Pregnancy, ruptured tubal, 30
Presence of a substance inhibiting the coagulation of the blood in anchylostoma, 173
Pulmonary tuberculosis, 88, 246

Radasch, H. E., exhibition of specimens, 3
Randolph, B. M., case of spontaneous arrest of growth in an endothelioma, 130
exhibition of specimens, 11
Ravenal, M. P., exhibition of specimens, 11
Report of committee on morbid growth concerning Dr. Stahl's specimen, 55
Résumé of literature relating to serum diagnosis, 97
Rhinophyma, specimen from a case of, 238
Riesman, David, discussion on aberrant pancreas, 230
exhibition of specimens, 12
remarks of, on a case of Filaria immitis in the heart of a dog, 92
Robertson, W. E., discussion on aberrant pancreas, 228
exhibition of specimens, 12
postpneumonic endocarditis, 199
Rosenberger, R. C., actual and comparative resistance of acid-fast bacilli, 19, 29
exhibition of specimens, 14
résumé of literature relating to serum diagnosis, 97
Ruptured tubal pregnancy, 30

Sailer, Joseph, carcinoma of the stomach with hyperacidity, 243
discussion on the changes in the intercostal muscles and diaphragm, 81
review of the recent literature upon the pathology of the liver, 33
Sarcoma of the bladder and prostate gland, 125
Scarlet fever, bacteriologic study of throats of, 201
Schamberg, Jay F., bacteriologic study of throats of cases of scarlet fever, 201
exhibition of specimens, 15
de Schweinitz, G. E., exhibition of specimens, 16
Scott, J. A., discussion on pancreatic hemorrhage, 54
Serum diagnosis, 97
Shumway, E. A., exhibition of specimens, 16, 18
Smith, A. J., discussion on a case of Filaria immitis in the heart of a dog, 94, 96
presence of a substance inhibiting the coagulation of the blood in anchylostoma, 173
Spiller, Wm. G., earlier changes in arteriosclerosis of the nervous system, 156, 172
exhibition of specimens, 16
Splenomegaly, case of, 44
Spontaneous arrest of growth in an endothelioma, 130
Springer, Harold L., clinical and pathologic reports, 229
Stahl, B. Franklin, pancreatic hemorrhage, 52, 55
Stanton, William B., aneurysm of the arch of the aorta mistaken clinically for pulmonary tuberculosis, 246
Stengel, Alfred, discussion on a case of xanthoma, 61
discussion on acid-fast bacilli, 55
discussion on aberrant pancreas, 230
discussion on coagulation of the blood in anchylostoma, 177
Stomach, carcinoma of, 243
wall of, accessory pancreas in posterior, 226
Stout, G. C., exhibition of specimen, 17
Swan, J. M., exhibition of specimen, 17

Tubal pregnancy, ruptured, 30
Tuberculosis, pulmonary, 88, 246
Tuberculous meningitis with congenital stricture of the rectum, 229
Trypanosoma diseases, 242

Urachus, cysts of, 125
Uremia with pericarditis, 229
Uremic hemiplegia, 62

Weisenburg, T. H., uremic hemiplegia, with changes in the nerve cells of the brain and cord, and recent primary degeneration of the central motor tract, 62
White, C. Y., exhibition of specimens, 17
Wieder, Henry, clinical and pathologic reports, 229
Willson, R. N., discussion on aberrant pancreas, 229

Xanthoma, case of, 56

Zimmerman, M. W. exhibition of specimens, 18

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NEW SERIES, VOLUME VIII.
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1883 Griffith, J. P. C., 1810 Spruce Street.
1897 Gross, Wm., 701 North Fortieth Street.
1890 Gummey, Frank B., 5418 Greene Street, Germantown.
1900 Gwyn, N. B., 23 South Twenty-first Street.

1893 Hamill, S. M., 1822 Spruce Street.
1893 Hand, Alfred, Jr., 1724 Pine Street.
1885 Hare, Hobart Amory, N. W. cor. Eighteenth and Spruce Streets.
1857 Harlan, G. C., 1515 Walnut Street (O. M.).
1902 Harland, W. G., 126 South Nineteenth Street.
1890 Hartzell, M. B., 3644 Chestnut Street.
1904 Hatfield, C. J., 256 South Eighteenth Street.
1901 Hawke, W. W., Philadelphia Hospital.
1900 Head, J., 1500 Locust Street.
1870 Henry, Frederick P., 1635 Locust Street.
1896 Henry, John M., 219 South Seventeenth Street.
1903 Herzberg, M., 512 North Sixth Street.
1880 Hewson, Addinell, Jr., 2120 Spruce Street.
1901 Hickman, W. A., 612 Pacific Avenue, Atlantic City.
1903 Hill, H. K., 1715 Spruce Street.
1899 Hitchens, A. P., Glenolden, Pennsylvania.
1902 Hodge, E. D., 346 South Fifteenth Street.
1899 Holloway, T. B., 49 North Fifty-second Street.
1905 Holmes, E. B., Municipal Hospital.

ELECTED

1905 Hosmer, C. M., 3949 Baltimore Avenue
1904 Hoyt, D. M., 3604 Chestnut Street.
1894 Hughes, George M., 241 North Eighteenth Street.
1882 Hughes, W. E., Fortieth and Chestnut Streets.
1904 Hume, J. E., 900 South Forty-ninth Street.
1901 Hunsicker, C. H., 1614 North Broad Street.
1902 Hunter, John W., 1934 Chestnut Street.

1901 Irwin, J. W., 1923 Vine Street.

1890 Jarrett, Henry, Broadway and Cherry Streets, Camden, N. J.
1904 Jenks, Horace H., 920 Clinton Street.
1895 Jopson, J. H., 334 South Sixteenth Street.
1898 Judson, Chas. F., 1539 Pine Street.
1899 Jump, H. D., 4634 Chester Avenue.

1898 Kalteyer, F. J., 214 South Fifteenth Street.
1901 Kane, J. A. B., 211 South Seventeenth Street.
1895 Kelly, A. O. J., 1911 Pine Street.
1905 Kelly, Thos. C., University Hospital.
1899 Kennedy, L. F., 301 Mauch Chunk Street, Pottsville, Pa.
1904 Kiefer, Charles, 1723 North Forty-second Street.
1902 Kinyoun, J. J., Glenolden, Pennsylvania.
1888 Kirby, Ellwood R., 1202 Spruce Street.
1900 Klapp, W. P., 1716 Spruce Street.
1890 Kneass, Samuel S., The Warwick, Nineteenth and Sansom Streets.
1898 Knipe, J. C., Diamond Street and Park Avenue.
1901 Kohn, B., 1325 North Thirteenth Street.
1895 Krusen, Wilmer, 127 North Twentieth Street.
1892 Kyle, D. Braden, 1517 Walnut Street.

1899 Landis, H. R. M., 130 South Twenty-third Street.
1890 Laplace, Ernest, 1828 South Rittenhouse Square.
1898 Latta, Samuel W., 3626 Baring Street.
1905 Lavenson, Ralph, S., 1342 Pine Street.
1894 Leach, W., Eastern State Penitentiary, Medical Department.
1869 Leaman, Henry, 828 North Broad Street.
1903 Lee, W. E., 823 North Twenty-fourth Street.
1888 Leidy, Joseph, 1319 Locust Street.
1905 L'Engle, Edward M., Twenty-third and Locust.
1887 Leopold, Isaac, 1520 Franklin Street.
1904 Leopold, S., 1632 Franklin Street.
1902 Levi, I. V., 1733 North Sixteenth Street.

ELECTED

1875 Lewis, Morris J., 1316 Locust Street.
1894 Lincoln, C. W., 5348 Wayne Avenue, Germantown.
1899 Lindauer, Eugene, 2018 North Thirty-second Street.
1886 Lloyd, James Hendrie, 3910 Walnut Street.
1898 Lodholtz, Edward, 3103 Diamond Street.
1903 Loeb, Leo, Medical Department, University of Pennsylvania.
1894 Loeb, Ludwig, 1421 North Fifteenth Street.
1902 Loeb, V. A., 1901 North Eighth Street.
1901 Longcope, W. T., 251 South Seventeenth Street.
1875 Longstreth, Morris, 1416 Spruce Street.
1903 Ludlam, S. D., Friends' Asylum, Frankford, Pa.
1903 Lukens, G. L., Fifth Avenue and Fayette Street, Conshohocken, Pa.
1902 Luther, J. W., 412 South Fifteenth Street.

1896 McCarthy, D. J., 1329 Spruce Street.
1904 McClarey, Samuel, 308 South Fifth Street.
1880 McClellan, George, 1352 Spruce Street.
1901 McConnell, G., 1618 Pine Street.
1904 McCoombs, R. S., 2113 Chestnut Street.
1892 McFarland, J., 442 W. Stafford Street, Germantown.
1902 McGowan, J. M., 406 South Broad Street.
1894 McKee, James H., 1519 Poplar Street.
1906 McLaughlin, J. J., 1532 South Fifth Street.
1898 McReynolds, R. P., 3722 Walnut Street.
1905 Maier, E. G., Philadelphia Hospital.
1905 Maier, F. Hurst, 2244 North Broad Street.
1902 Marshall, C. J., 2004 Pine Street.
1899 Masland, M. C., 2134 North Nineteenth Street.
1873 Meigs, Arthur V., 1322 Walnut Street.
1906 Meyers Milton K., 2134 North Eighteenth Street.
1878 Mills, C. K., 1909 Chestnut Street.
1884 Mitchell, J. K., 1730 Spruce Street.
1896 Modell, D. A., 242 Fairmount Avenue.
1904 Moore, Joseph A., 146 Richmond Street.
1904 Moorehouse, G. R., 2033 Walnut Street.
1898 Morris, Henry, 313 South Sixteenth Street.
1885 Morrison, William H., 1821 Frankford Avenue, Holmesburg, Pa.
1887 Morton, S. W., 1933 Chestnut Street.
1899 Müller, G. P., 1626 Spruce Street.
1880 Musser, J. H., 1927 Chestnut Street.

1879 Neff, J. S., 2300 Locust Street.
1903 Nesbit, V., 908 Pine Street.
1900 Newlin, A., 1702 Pine Street.

ELECTED

1898 Newton, R. D., 6137 Vine Street.
1902 Noble, C. P., 1509 Locust Street.
1900 Norris, Geo. W., 1530 Locust Street.

1894 O'Malley, Joseph, 2228 South Broad Street.
1900 O'Reilly, C., 1240 Erie Avenue.
1897 Ostheimer, Maurice, 225 South Twentieth Street.

1893 Packard, F. R., 1831 Chestnut Street.
1857 Packard, John H., Hotel Stenton (O. M.).
1900 Pancoast, H. K., University Hospital, University of Pennsylvania.
1901 Patterson, F. D., 2103 Locust Street.
1900 Pearson, L., Veterinary Department, University of Pennsylvania.
1903 Pemberton, R. 346 South Sixteenth Street.
1897 Pepper, William, 1811 Spruce Street.
1895 Perkins, F. M., 1428 Pine Street.
1897 Peter, L. C., 2136 Oxford Street.
1902 Pfahler, G. E., 1409 Spruce Street.
1901 Pickett, W., 124 South Eighteenth Street.
1885 Piersol, G. A., 4724 Chester Avenue.
1905 Piersol, Geo. M., University Hospital.
1890 Potts, C. S., 1733 Chestnut Street.
1900 Prince, D. H., Jefferson Medical College.
1901 Purves, G. M., 750 South Tenth Street.

1904 Rabt, Walter C., 309 South Sixteenth Street.
1905 Radasch, H. E., 914 South Forty-seventh Street.
1901 Ranck, E. M., 107 Maine Street, Natchez, Miss.
1885 Randall, B. A., 1717 Locust Street.
1898 Ravenel, M. P., 908 Pine Street.
1904 Reber, Wendell, 1212 Spruce Street.
1894 Reckefus, C. H., 506 North Sixth Street.
1899 Reynolds, W., 27 South Indiana Avenue, Atlantic City.
1894 Rhein, J. H. W., 1732 Pine Street.
1903 Rhein, R. D., 2016 Pine Street.
1904 Rhoads, J. E., 2101 Chestnut Street.
1904 Rivas, Damaso, 5927 Girard Avenue.
1894 Riesman, David, 1624 Spruce Street.
1891 Ring, G. O., S. W. corner Nineteenth and Chestnut Streets.
1876 Roberts, John B., 313 S. Seventeenth Street.
1884 Robertson, W. E., 320 South Sixteenth Street.
1902 Robins, Albert, 427 Brown Street.
1901 Robinson, E. T., 1326 Pine Street.

ELECTED

1904 Robinson, G. Canby, Pennsylvania Hospital.
1889 Robinson, William Duffield, 2012 Mount Vernon Street.
1899 Rodman, W. L., 1904 Chestnut Street.
1903 Roe, W. J., 1210 Locust Street.
1905 Royer, Franklin B., Municipal Hospital.
1898 Rosenberger, R. C., 2330 North Thirteenth Street.
1894 Ross, George, 1721 Spruce Street.
1900 Roussel, A. E., 2112 Pine Street.
1900 Roxby, J. B., 2222 North Nineteenth Street.

1905 Salus, H. W., 337 South Twelfth Street.
1904 Sargent, A. Alonzo, 939 Spruce Street.
1896 Sailer, Joseph, 248 South Twenty-first Street.
1890 Sartain, Paul J., 212 W. Logan Square.
1895 Schamberg, J. F., 1922 Spruce Street.
1882 de Schweinitz, G. E., 1705 Walnut Street.
1904 Schumann, E. A., 15 Pelham Road.
1902 Schwerin, Justin C., 1625 Diamond Street.
1890 Scott, J. A., 1834 Pine Street.
1898 Sharpless, Wm. T., 100 South Church Street, West Chester, Pa.
1902 Shields, W. G., Jr., 412 West School House Lane, Germantown.
1905 Shoemaker, Hanlan, 209 South Seventeenth Street.
1889 Shoemaker, Harvey, 2011 Chestnut Street.
1895 Shumway, E. A., 2007 Chestnut Street.
1899 Sinclair, J. F., 4103 Walnut Street.
1904 Singer, Benjamin L., 1914 North Eighteenth Street.
1902 Sinkler, Francis W., 348 South Sixteenth Street.
1868 Sinkler, Wharton, 1606 Walnut Street.
1901 Siter, E. D., 2038 Locust Street.
1881 Skillern, P. G., 241 South Thirteenth Street.
1904 Skillern, Penn-Gaskell, Jr., 241 South Thirteenth Street.
1903 Small, J. H., 914 South Forty-eighth Street.
1903 Smith, A. J., Medical Department, University of Pennsylvania.
1898 Smyth, Henry Field, Odessa, Delaware.
1902 Somers, L. A., 3554 North Broad Street.
1905 Speese, John, 1342 Pine Street.
1894 Spellissy, Joseph M., 110 South Eighteenth Street.
1896 Spiller, William G., 4409 Pine Street.
1904 Stadelman, Eugene, Sta. Maria Del Oro, Dgo.
1904 St. John, E. Q., 1833 Chestnut Street.
1890 Stahl, B. F., 1727 Pine Street.
1901 Stanton W. B., 732 Pine Street.
1894 Steele, J. D., Fortieth and Locust Streets.
1886 Stengel, Alfred, 1811 Spruce Street.

ELECTED

1900 Stetson, J. B., 1329 Spruce Street.
1889 Stevens, Arthur A., 314 South Sixteenth Street.
1896 Stewart, Alonzo H., 250 North Twelfth Street.
1904 Stilwagon, Thomas, Jr., Jefferson Medical College Hospital.
1899 Stout, G. C., 1726 Chestnut Street.
1905 Stout, Philip S., Fifth Street and Greenwood Avenue.
1884 Stritmatter, I. P., 999 North Sixth Street.
1869 Stryker, Samuel S., 3833 Walnut Street.
1894 Swan, John M., 3713 Walnut Street.

1900 Talley, J. E., Fifty-sixth Street and Lansdowne Avenue.
1895 Taylor, A. E., University of California.
1897 Teller, Wm. H., 1713 Green Street.
1894 Thomas, W. Hersey, 1445 North Seventeenth Street.
1894 Thomson, Archibald G., 1426 Walnut Street.
1868 Thomson, William, 1426 Walnut Street.
1902 Thornton, E. Q., 922 Spruce Street.
1899 Tinker, M. B., Johns Hopkins Hospital, Baltimore, Md.
1902 Tracy, S. E., 1415 Walnut Street.
1897 Tucker, Henry, 112 South Twenty-first Street.
1898 Twaddell, Thomas, 4203 Chester Avenue.
1863 Tyson, James, 1606 Spruce Street.
1890 Tyson, T. Mellor, 1506 Spruce Street.

1900 Uhle, A. A., 1327 Jefferson Street.
1904 Ullman, J. T., 24 Carpenter Street, Germantown.

1895 Vandervoort, C. A., 3311 North Broad Street.
1887 Vansant, Eugene L., 1929 Chestnut Street.
1905 Van Kaathoven, J. A. A., 1715 Spruce Street.

1898 Wadsworth, W. S., The Covington, Thirty-seventh and Chestnut Streets, West Philadelphia.
1903 Walker, J. K., Pennsylvania Hospital.
1891 Wallace, James, 350 South Sixteenth Street.
1899 Walsh, J. P., 732 Pine Street.
1904 Walter, Georgianna, 1624 Pine Street.
1890 Warder, C. B., 1715 Walnut Street.
1903 Weisenburg, T. H., 2030 Chestnut Street.
1887 Westcott, T. S., 1833 Spruce Street.
1902 Wetherill, H. E., 3734 Walnut Street.
1897 White, Courtland Y., 1808 Diamond Street.
1873 White, J. William, 1810 South Rittenhouse Square.
1901 Whiteway, Harold M., 1924 Chestnut Street.

ELECTED

1893 Whiting, A. D., 1523 Spruce Street.
1905 Wieder, Henry S., 2131 North Fifteenth Street.
1868 Willard, De Forest, 1818 Chestnut Street.
1898 Willson, R. N., 1708 Locust Street.
1869 Wilson, James C., 1437 Walnut Street.
1891 Wilson, Samuel M., 1517 Arch Street.
1891 Wilson, W. R., 112 South Twentieth Street.
1901 Winsor, Henry, in care of Winsor & Co., Piers 18 and 20, South Delaware Avenue.
1900 Wister, J. W., 5430 Germantown Avenue.
1890 Wood, A. C., 128 South Seventeenth Street.
1906 Wood, Harold B., 5038 Pine Street.
1898 Wood, George B., 129 South Eighteenth Street.
1865 Woods, D. Flavel, 1501 Spruce Street.
1899 Worden, C. B., 4208 Walnut Street.

1897 Yarrow, Thomas J., Jr., The Walter Farm, Cape May, N. J.

1902 Zimlick, A. J., 6236 Woodland Avenue.
1895 Zimmerman, Mason W., 1522 Locust Street.

NON-RESIDENT MEMBERS.

Baines, A. S., Jr., 4484 Finney Avenue, St. Louis, Mo.
Ball, M. V., Warren, Pa.
Breinig, P. B., Bethlehem, Pa.
Carter, W. S., Galveston, Texas.
Cerna, D., Galveston, Texas.
Dock, George, Ann Arbor, Mich.
Edwards, W. A., San Diego, Cal.
Egbert, Joseph P., Wayne, Delaware County, Pa.
Eskridge, J. T., Denver, Col.
Fox, J. M., Torresdale, Pa.
Gaylord, H. R., Buffalo, N. Y.
Gerson, T. P., 1621 Ingraham Street, Los Angeles, Cal.
Hamaker, W. D., Meadville, Pa.
Hamann, C. A., 517 Euclid Avenue, Cleveland, Ohio.
Harris, H. F., Atlanta, Georgia.

Harrison, W. H., Harrisburg, Pa.
Hatch, John L., 2010 Fifth Avenue, New York City.
Hileman, J. B., Altoona, Pa.
Hiller, H. H.
Holder, C. A., Colorado Springs, Col.
Howard, F. H., Williamstown, Massachusetts.
Hunt, J. R., New York.
Izard, W., Camden, New Jersey.
Jamar, John H., Elkton, Md.
Lincoln, W. R., Cleveland, Ohio.
Muhlenberg, Frank, Reading, Pa.
Nancrede, C. B., Ann Arbor, Mich.
Osler, William, University of Oxford, England.
Pease, H. D., Buffalo, N. Y.
Pfouts, G. B., Morris Plains, N. J.
Powell, W. M., Atlantic City, N. J.
Rahter, C. A., Harrisburg, Pa.
Rivas, Damoso, Lille, France.
Schreiner, E. R., U. S. A.
Slifer, Henry F., North Wales, Pa.
Smith, Allen J., Galveston, Texas.
Stadelman, E., Durango, Mexico.
Stiles, G. A., Conshohocken, Pa.
Stubbs, R. P., Wilmington, Delaware.
Taylor, A. E., University of California, San Francisco, California.
Taylor, L. H., Wilkesbarre, Pa.
Toulmin, H., Haverford, Pa.
Wells, G. M., Wayne, Delaware County, Pa.
Wetherill, R. B., Lafayette, Ind.
White, Frank, Elwyn.
Williams, H. L., Minneapolis, Minnesota.
Wilmarth, A. W., State Home for the Feeble-minded, Chippewa Falls, Wisconsin.
Yates, J. L., Ellis Avenue, Chicago, Ill.
Ziegler, J. L., Mt. Joy, Pennsylvania.

CORRESPONDING MEMBERS.

ELECTED

1866 Bumstead, Freeman J. Deceased.
1859 Clark, Alonzo, New York. Deceased.
1898 Cornil, V., Faculté de Médecine, Paris, France.
1859 Dalton, J. C., New York. Deceased.
1885 Dent, Clinton T., Assistant Surgeon and Lecturer on Practical Surgery at St. George's Hospital, Surgeon to Belgrave Hospital for Children, London, England.
1860 Ellis, Calvin. Deceased.
1888 Fedeli, Gregorio, Rome, Italy.
1858 Flint, Austin, Sr. Deceased.
1890 Gibbes, Heneage, Ann Arbor, Michigan.
1858 Hammond, William A., New York. Deceased.
1860 Isaacs, Charles E., Brooklyn. Deceased.
1878 Jackson, J. B. S., Boston. Deceased.
1886 Pye-Smith, P. H., Physician and Lecturer on Medicine at Guy's Hospital, London, England.
1860 Reeves, James E., Wheeling, West Virginia. Deceased.
1861 Rokitansky, Carl. Deceased.
1898 Virchow, Rudolf, Berlin, Germany. Deceased.
1860 Watson, John, New York. Deceased.
1898 Welch, William H., Professor of Pathology, Johns Hopkins University, Baltimore, Maryland.
1859 Worthington, Wilmer, West Chester, Pennsylvania. Deceased.

Proceedings

of the

Pathological Society of Philadelphia.

JANUARY, 1905. NEW SERIES, VOL. VIII., NO. 1

TABLE OF CONTENTS.

VAUGHAN, The Use of Food Preservatives.—COPLIN, A Cabinet for Investigating the Action of Vaporizable and Gaseous Disinfectants and Insecticides, and for Teaching Disinfection to Students.—MCCONNELL, Supernumerary Anterior Extremities in a Frog.—FUNKE, Erosive Gastritis.

The Use of Food Preservatives.

BY VICTOR C. VAUGHAN, M.D.,
ANN ARBOR, MICH.

Discussion by DR CHARLES HARRINGTON, of Boston, Mass., and DR. C. B. COCHRAN, of West Chester, Pa.

INASMUCH as the succession of seasons, the intervals between harvests, and great distances from sources of supply compel man to store and transport many food products, and since these are more or less perishable, the desirability and the necessity of artificially preserving these foods from decay and from putrefaction are apparent; and certain agents have been used for this purpose from prehistoric times. Common salt, or sodium chloride, has priority in point of time, and potassium nitrate, or saltpetre, has the sanction of long-continued use, although I am not sure that the unrestricted use of the latter is altogether free from harm. Primitive man, in all probability, learned from observation that meat exposed to the smoke of his campfire did not become putrid so quickly as meat not so treated. Sterilization and canning are of comparatively recent introduction, but now of wide application. Refrigeration finds frequent new adaptations, and

the machinery employed in securing it has been developed and improved from year to year.

The relatively new science of bacteriology has demonstrated that the processes of decay and of putrefaction are due to the growth and multiplication of low forms of life and that the preservation of foods depends on the exclusion or retardation of the growth of bacteria. The rapid development of chemistry has led to the discovery and inexpensive preparation of a long list of chemical bodies possessed of more or less powerful germicidal properties, and the purveyors of food products have not been slow to utilize these scientific discoveries. Some of these chemicals used in the preservation of foods are, to say the least, questionable in their effects on the life and health of the food consumer. This fact has induced sanitarians to invoke the passage of legal enactments to control and to regulate their employment, and many of the States of the Union now have what are known as pure food laws and have provided officials whose function it is to enforce them. Courts of justice, in the execution of these laws, frequently call in medical men who have given especial attention to these matters and ask from them information concerning the harmfulness or harmlessness of the chemical compounds employed by dealers in foods. In this way it has happened that medical men are frequently asked to serve as experts in deciding questions involved in the administration of the pure food laws. From his knowledge of the human body in health and disease, and of the effects of various chemical compounds on physiologic processes, the medical man is supposed to be qualified above others in giving testimony along these lines.

The questions that may arise legitimately in trials for the violation of the pure food laws are many and varied. In part they are chemical, inasmuch as the nature of the compound employed and the various reactions into which it may enter, when brought into contact with the fluids and tissues of the body, must be comprehended and explained to a jury made up of men, who, as a rule, have had no training in chemical science. In part the questions are bacteriologic, for it must be known whether or not the substance has any germicidal properties and, if it has, if it acts on all bacteria alike. Is it effective to the same extent on aërobic and anaërobic germs, and on the relatively harmless and the toxicogenic? Much hinges on this question, as I will attempt

to show later. The questions likely to come up also involve physiologic and pathologic knowledge. Food preservatives, if largely used, will be consumed not only by the healthy and robust, but by those with every form of disease, both acute and chronic. The dyspeptic, the neurotic, the diabetic, the nephritic, as well as the healthy man, must be considered in deciding whether or not a given chemical compound should be permitted as a food preservative. The infant and the aged, as well as those in the prime of life, are involved. If formaldehyde is to be permitted as a milk preservative it must be remembered that it will be largely consumed by infants, and not only by healthy infants, but by those suffering from gastrointestinal disturbances; by the dyspeptic and rachitic, as well as the vigorous. If salicylic acid is to be used as a beer preservative, it must be borne in mind that it will be consumed not only by the man who takes an occasional glass, but also by the one who is given to frequent and deep potations. The food preservative that receives legal sanction must be harmful to none of these, for it is the duty of the State to protect all alike, and because a man is killing himself by excessive beer drinking this is no reason why his death should be hastened by the addition of salicylic acid to his favorite drink.

One question which the expert should always ask himself, even if it be overlooked by both prosecution and defence, may be stated as follows: Is the substance in question a real preservative or only apparently such? If this question could be scientifically answered, it would at once settle the claims of a considerable number of the preparations now in use. A true food preservative is a substance which when added to food in the fresh state keeps it in a wholesome condition for a considerable period of time. This is true of common salt, saltpetre, and of certain constituents of wood smoke. It is too much to expect that preserved food shall be as toothsome, as easily digested, and as easily assimilated as the same food in the fresh state, and although this is accomplished with certain foods and with certain preservatives it can hardly be expected in all cases. Bacon is believed to be fully as pleasing to the taste, more easily digested, and quite as readily assimilated as fresh pork, but this is not true of corned beef, nor of preserved fruits and vegetables.

A true food preservative must keep the substance to which it is

added in a wholesome condition, so that it can be consumed by persons in every physical condition of life without impairment of health or danger to life. It is not the function of a food preservative to impart to the food a deceptive appearance and to make it look better than it actually is. The law takes special cognizance of this point, and plainly forbids all articles of this class, and I am sure that this law is wise. This excludes all meat preservatives that restore the color and fresh appearance to partially decomposed meats. Moreover, it is not the function of a true food preservative simply to preserve the fresh appearance while putrefactive changes go on, at least without marked and sufficient hindrance. To prevent the development of those bacteria that produce odoriferous substances while the more toxic bacteria that develop no telltale odor continue to grow and multiply does not comply with the requirements demanded by a food preservative that asks for legal sanction. It follows from this that we should be informed not only in a general way concerning the antiseptic properties of the substances in question, but we must know something of its specific action on toxicogenic as well as non-toxicogenic bacteria. To retard the multiplication of the lactic acid bacillus and thus to prevent the souring of milk, while colon bacilli continue to multiply uninterruptedly, is not the function of a true food preservative. Such food preservatives are wisely condemned by legal enactment. They take down the danger signal, but do not remove the obstruction in the road.

Some esthetic individual might contend that the red lights along the streets do not look well on a dark night, so he removes the lanterns, but leaves the stone piles and open ditches to wreck vehicles and endanger lives. Should such a man be considered a benefactor to his race, or a dangerous lunatic?

From experiments made in my laboratory, I can state that the addition of formaldehyde to milk in quantities varying from 1 : 25,000 to 1 : 50,000 retards the growth of the lactic acid bacillus, and thus delays the souring of milk, while it has but little effect on the multiplication of colon and typhoid bacilli. The most ignorant mother knows enough not to give her babe sour milk, but even the most intelligent mother might give the formaldehyde milk, laden with its poison-producing bacteria, because, so far as she can judge by appearance

and taste, it is all right. The man who adds formaldehyde to his milk takes down the danger signal, but does not remove the danger. Is he a philanthropist or is he guilty of manslaughter when the child fed on this milk dies? In cases of this kind, it matters not whether the preservative is directly, and in and of itself, harmful to the human body or not, its use should be prohibited. I am by no means sure that formaldehyde in the quantities in which it is used in milk is, in and of itself, of great harm to the body of man, but I am convinced that its use in milk, especially in that fed to infants, is very properly condemned by the laws of many States. Bacteriologists have found that sodium sulphite is possessed of but feeble germicidal properties, and yet we know that practically it does preserve the color and delay the development of putrefactive odors in meat for a relatively long time. It is more than probable that a careful investigation of this apparent contradiction will show that this substance, like formaldehyde, retards the growth of the non-toxicogenic rather than of the toxicogenic bacteria. However, this point deserves patient and prolonged investigation, and the laboratories of our agricultural colleges might carry out many series of experiments along this line, varying the conditions from time to time, taking into consideration the character of the food employed, the species of bacteria present, the temperature, time, etc. There is opportunity here for research that may prove not only instructive, but of practical value.

So-called preservatives that remove the danger signal and leave the danger untouched should be condemned, whether it can be shown that the substance employed is a poison or not. Even the most inert body belonging to this class should not be used, and certainly not in food fed to children, so large a proportion of whom die from milk poisoning.

Inquiry into the effect of the substance in question on the digestive fluids and processes is legitimate in considering the claims of any food preservative, and in making this inquiry it must not be forgotten that the preservative, if permitted, will be taken by those with every degree of digestive impairment as well as by the most vigorous. Neutralization of the free hydrochloric acid of the gastric juice is a matter of no little importance, as every physician who has made many analyses of gastric contents can appreciate, and the action of the substance on

the digestive enzymes is probably of still greater importance. The digestive organs are the laboratories in which the nutritive parts of the food are fitted for absorption and assimilation; and interference with the normal processes of the alimentary canal mean, sooner or later, disaster to every organ of the body. The most general and superficial knowledge of chemistry suffices to indicate that sodium sulphite will neutralize the free hydrochloric acid of the stomach, and a simple calculation, based on the amount of this substance which may be found in the food, will show the volume of acid that may be neutralized. It matters not whether the acid radicle of the sodium sulphite is split off in the stomach as the anhydride or immediately combines with water to form sulphurous acid, the effect is practically the same. I was somewhat startled recently, however, to learn from the testimony of an expert that the stomach is a tank always filled with free oxygen, and this immediately converts the sodium sulphite into sodium sulphate, which, as all must admit, in the quantity employed can be of little effect, even on the dyspeptic. The investigation of the effects of preservatives on the digestive processes should be made outside the body, where they can be exactly determined. They should be made with each ferment and then with combinations. Numerous studies of this kind have been made with some food preservatives, for instance, with formaldehyde, and it seems to be well established that this substance markedly interferes with the action of some of the digestive enzymes. The defence frequently attempts to belittle testimony showing the retardation of the digestive processes by the substance in question, and the expert is asked what harm it will do to have some of the acid of the gastric juice neutralized by the little sodium sulphite in a Hamburg steak eaten once a week? This question is an attempt to mislead and to convey to the jury the impression that the matter is of but trifling import and that the expert is trying to build a fortress of straws. However, if a man has sodium sulphite in his meat, alum in his bread, and formaldehyde in his milk, it may seriously be questioned if his gastric juice, or what little he has left of it, will suffice to convert the proteids of his food into peptones.

The question of the possible poisonous action of the preservative must always be considered and is frequently of primary importance. There seems to be great diversity of opinion among medical men

concerning what constitutes a poison. Some appear to think that before a chemical compound can be classified as a poison it must be capable of causing death in the quantities used in food, or that at least it must visibly and grossly disturb the health of man in a few hours. If it fails to do this it is not a poison, or at least in the quantity employed it should not be so designated. I have regarded this question quite differently, and I will attempt to give, in a few words, my ideas on this point. The bodies of animals, including man, are made up of cells that are alive and perform duties the proper performance of which is necessary to the well-being of the whole of the individual. These cells are essentially chemical compounds and those substances which combine with these cells chemically in such a way as to cause their destruction or to render the performance of their normal functions impossible are poisons. Therefore, a poison may be defined as a substance that destroys or impairs cell function by virtue of its chemical constitution. The cells of the different organs vary more or less in chemical composition, and consequently a compound may react with a liver cell more readily than it does with a muscle, bone, or nerve cell. In this way poisons are, to a certain extent, selective in their effects, their selective action being dependent on the readiness with which they react with the chemical constituents of different cells. A substance that combines with and consequently interrupts the function of the cells of the respiratory centre in the brain causes the speedy death of the individual, while those substances that destroy blood, liver, or kidney cells are slow poisons, inasmuch as the life of the individual may survive the destruction of a large number of these cells, but those of one class are just as truly poisons as those of the other. Potassium chlorate reacts with the hemoglobin of the blood, converting it into methemoglobin, and if the number of red blood cells destroyed is sufficiently great to impair the action of the other cells, especially those in the vital centres of the brain, death of the individual occurs. On the other hand, if the number of injured blood cells be not so great, life is not destroyed, but health is impaired.

Chloroform, ether, and other anesthetics combine with and temporarily paralyze the nerves of sensation. Ethyl alcohol, besides its effects on the nervous system, leads to alterations in hepatic cells, and cirrhotic changes are induced; while methyl alcohol finds its

special affinities in the ganglion centres of the retina and in the optic nerve. Many of the metals have their most marked effect on the renal cells and some have a special action, apparently, on connective-tissue cells. In the pathologic laboratory potassium bichromate is employed on animals for the specific purpose of developing nephritis. There are other illustrations, but these, I hope, will suffice to make clear my position. All poisons are such because they destroy or impair the action of certain cells of the body, and the immediate effect on the life of the individual depends on the kind and number of cells put out of commission.

The question of dose cannot be left out of consideration in the study of poisons, because a certain relatively small number of cells, in most organs of the body at least, can be destroyed without any appreciable result. Moreover, the quantity or dose given determines, to some extent, the cells affected; thus, the introduction of from 5 to 10 grams of sodium sulphite into the stomach of a rabbit at one dose causes death in a few minutes, while the administration of the same substance in much smaller quantities just as certainly kills, but a longer time is required. When a large single dose is given, some of the unchanged sulphite reaches the brain, and the cells of the respiratory centre are so injured that respiration stops, and death occurs almost instantaneously.

When smaller doses are given, all the sulphite is used up before it reaches the brain, especially in the walls of the stomach and in the blood. Digestion and assimilation are impaired, emaciation follows, and in time death ends the process. Is not sodium sulphite just as truly a poison in one case as in the other? But, it is asked, is not nearly everything a poison if given in sufficient quantity? And the expert is frequently asked if common salt is not a poison in large doses; it may kill, but it is not a poison. The injection of concentrated solutions of salt or of sugar, or even of distilled water, directly into the blood may kill by altering the specific gravity of the plasma, but these are not poisons. If the stomach of a rabbit is filled with a saturated solution of common salt speedy death results, but this is due to physical causes and to the absorption of water, and is not due to the chemical combination of salt with the cells of the body. Broken glass or splinters of steel taken into the stomach may kill the individual, and molten

metal poured into the throat would have a like effect, but these are not poisons because their injurious effects are due to physical and not to chemical causes.

Should the fact that a substance is a poison prohibit its use as a food preservative? Admit that a substance is a poison and it must also be admitted that its use as a food, or in a food, must be sanctioned by long-continued custom or must be regulated by law. I think that this is the holding of eminent jurists in all parts of the civilized world. I believe that the higher courts of Pennsylvania have held that it is sufficient to show that the substance is a poison, and that it is not necessary to show that the quantities employed are dangerous, and this decision is certainly a wise one. In cases of trial for murder by the administration of poison, it has been generally held that it is not necessary for the chemist to recover from the body a poisonous dose, but simply to show the presence of poison. People in general are not legally qualified to administer poison to others. Members of the medical profession only are legally qualified for this purpose, and it is for this reason, in part at least, that the State assumes the right to specify within certain limits the qualifications of the physician.

If sodium sulphite is a poison, and if the only safeguard in its use as a food preservative is in the amount added to the food, shall this be left to the vendor, who is ignorant of the chemistry and toxicology of the compound and whose sole object is to make his goods look more attractive to the buyer? If this compound is to be legally sanctioned as a food preservative, the law must determine in what quantities it may be employed, and it must select qualified men to mix the preservative with the food. The statutes specify the qualifications of the physician who prescribes and of the pharmacist who prepares this and other poisons when given as medicines, and is it not of more importance that the addition of poisons to our daily foods should be conducted under similar safeguards? Medical experts may differ in opinion concerning the classification of a given compound as a poison, but if the court be convinced that it is a poison, and that the possibility of doing harm with it depends on dosage, it is not probable that its usage will receive legal sanction. Poisons should be sold only under strict legal restrictions; the experience of all ages has demonstrated the wisdom of this. The cases of poisoning with chromate of lead, so

admirably worked up some years ago by Stewart, of Philadelphia, will illustrate what harm the cupidity of the vendor and the ignorance of the user may accomplish. The fact that the substance in question has been largely employed in medicine, and sometimes with beneficial results, is often brought out in court. In my opinion, testimony of this kind is of but little value and is capable of being misinterpreted. The physician, in order to cure a syphilitic lesion, very properly takes the risk of doing harm to the kidneys by the administration of mercury, but this does not indicate that mercurial compounds are harmless or that they may properly be used as food preservatives. This point leads to such absurdities that I am ashamed to pursue it further, and yet in two cases tried in Pennsylvania recently medical men have used it in defence of food preservatives. Along the same line is the question of poisonous dose, and the expert finds in some medical book that the medicinal dose is much greater than the amount one would take at a meal, or in one day, or possibly in one week. In regard to this point, it is only necessary to state that there is probably no poisonous drug that has been in use for ten years or longer for which you cannot find in some book the medicinal dose given at a figure considerably beyond the limit of safety.

There is another line of testimony sometimes given that seems to me to be of questionable value; an expert testifies that foods containing a certain preservative have been eaten by men in Alaska or in some other place remote from sources of food supply without recognizable harm. Men so situated must eat what they can get; but here at home we are not driven to such a choice. Men in remote places have eaten dogs and have pronounced the repast enjoyable, palatable, and nutritious; but this would hardly justify a butcher in sending a canine tenderloin when a beefsteak had been ordered.

The source of one's knowledge concerning the action of poisons is a matter deserving consideration. Lately there has been a tendency on the part of some to question toxicologic knowledge gained by animal experimentation and to offer instead observations of the effects on man. One expert has tested the action of a substance on the lower animals, which he has fed for a certain time and which he has then killed, either by the continued administration of the drug or otherwise; and after death he has made careful macroscopic and micro-

scopic studies of the different organs. From these studies he has arrived at certain conclusions. The opposing expert states that he has prescribed the substance in question for malaria or for some other disease to a large number of people and without injury, possibly with benefit. Which kind of testimony is the more scientific and valuable? We will suppose that the action of potassium bichromate is in question. I take this substance because it has not, so far as I know, been used as a food preservative, although a more poisonous chromate, that of lead, has been employed in Philadelphia as a food adulterant. One man testifies that, following the method of Gunzberg, he has prescribed the bichromate to his syphilitic patients and that it has done them no harm. Another says that he has tested the action of this substance on dogs and that he finds it induces certain distinct lesions, especially in the kidneys. Which line of evidence is the more satisfactory, and, after hearing both, to which shall we give the greater weight in coming to a conclusion concerning the action of the bichromate? For one, I should not long hesitate in coming to a decision, and I leave others to decide for themselves, but while they are doing so I beg leave to ask a few questions. Which, the syphilitic or the dog, was in health to start with? To which has the substance been administered most certainly in the quantities claimed? Which has been more completely under the control and observation of the administrator? and, when both die, in which is the cause of death most unquestionable? Moreover, suppose that the kidney lesions are found in both, is it not true that there might be grave and honest doubt as to what caused them in the man? The conditions under which most patients live are too complex for them to serve in our observations concerning the actions of poisons. Dr. Wiley, at Washington, is now testing the action of certain food preservatives and adulterants on men, and, inasmuch as these men are under his control and have their lives regulated by his rules, we may be sure that valuable information will be secured, but toxicologic experiments on men under the most favorable conditions will need to be supplemented by animal experiments. The microscopic lesions induced in the organs can be ascertained in no other way. We must be able to kill the animals after they have received definite quantities of the substance and to study their tissues, both macroscopically and microscopically.

In conclusion, I will state what I believe should be the essentials of a substance before its employment as a food preservative should receive legal sanction.

1. It must be a real preservative, keeping the food in a wholesome condition and not merely retaining the appearance of freshness while bacterial changes continue.

2. In the largest quantities used, it must not materially impair any of the digestive processes.

3. It must not be a cell poison, or, if a cell poison in any amount, it must be added to foods only by persons qualified by special training and officially authorized, and foods containing these substances must be plainly labeled and the kind and amount of the preservative used must be made known not only to the buyer, but to each consumer.

Discussion.

Dr. Charles Harrington: The question has two very important sides: first, we have to consider the enormous commercial interests involved; second, the vastly more important matter of possible injury to the public health.

The commercial importance of chemical preservation of foods is admitted by everybody, and that part of the subject can, therefore, be dismissed. Concerning the possible injury to the public health, there is great dispute. Those who have given the subject much attention may be divided into several groups: 1. Those who would prohibit all chemical preservatives, excepting salt, sugar, alcohol, vinegar, the products of smoke, and, perhaps, saltpetre. 2. Those who would prohibit absolutely a certain small number, as boric acid, borax, sulphites, fluorides, and salicylic acid. 3. Those who would prohibit none at all, in the belief that none of them is capable of inducing injury in the small amounts likely to be ingested. 4. Those who, while objecting to their use in milk, would permit them to be added to all other foods. 5. Those who would permit the use of any preservative, provided the customer is notified of its presence.

Those who would not restrict the employment of the common preservatives assert the absence of convincing proof that this or that substance used can harm the human system. They point to the fact that one and all are employed in one way and another in the treatment

of the sick. I have heard this argument countless times. I have heard it urged that copper salts, used for improving the color of canned vegetables, are tonic in their action; that salicylic acid is beneficial to the rheumatic; that borax and boric acid are useful as applications to various mucous membranes; that the sulphites are of value in certain digestive disturbances; and if they but had some preservative action, we should doubtless hear similar arguments defending the use of strychnine, aconite, and arsenic. True, we never hear of acute symptoms traceable to the ordinary preservatives. The reasons are simple. In the first place, no sane man would think of treating his merchandise in such a way that it would make the consumer acutely sick: that would be the last method he would think of adopting to make his wares popular. He must use something which will accomplish the desired end without impairing palatability and without calling the consumer's attention to its presence. Because a drug in certain small doses causes no perceptible disturbance of function, can we say that its long-continued use may not bring about degenerative changes whose cause cannot accurately be determined? Has anybody ever known acute symptoms to be caused by a single drink of water containing a minute dose of oxycarbonate of lead, or by a hundred or more such doses? No acute disturbance is ever thereby caused, however many such drinks are taken, but I venture to say that there is not one present who has not seen a number of persons who know to their sorrow that chronic poisoning can thereby be caused, and that its effects are lasting. May it not be so with some of the preservatives in common use, which have able and eloquent defenders? It takes a long time in some cases to show that a drug which is launched only after much careful pharmacologic experimentation is not wholly free from objectionable properties, and why should not the same hold true of drugs that are used in foods?

Suppose one feels ill—has heartburn, headache, and diarrhea—who is likely to attribute the disturbance to some article of food, about the abnormal chemistry of which he knows nothing? How is he or his physician to know that the ham, or the corned-beef, or the oysters that he ate for luncheon in a down-town restaurant contained several grams of borax and boric acid, or that the ale that he drank therewith contained a large dose of calcium bisulphite? Is either of them likely

to think of such possibilities, when it is so much easier to attribute the disturbance to "taking cold," or "being bilious," or to an idiopathic dyspepsia?

When a physician tries a new drug, he proceeds with all proper precautions and with careful regulation of the dose; but the food-preserver is not a scientist. He knows nothing of pharmacology; his object is not to benefit the consumer, but to extend the commercial life of his merchandise; he has no knowledge of the condition of the stomach into which his preservative drug is to be introduced, nor whether it belongs to a strong man, an invalid, or a child; and he uses the public as experimental animals without its knowledge or consent. The consumer, ignorant of the fact that he is a test-object, if made sick by a large dose, may blame his food, but not the preservative which it contains; or he may blame himself for overeating or eating when he was too tired; or he may attribute his trouble to the concomitant drink, but he has no thought of borax, boric acid, and sulphites. Personally, I object to being a test-object for a butcher's experiment. Moreover, I was taught in my student days not to write shot-gun prescriptions. I do not care for the daily ingestion of consecutive or simultaneous doses of borax, boric acid, salicylic acid, benzoate of sodium, formaldehyde, sodium sulphite, calcium bisulphite, and calcium fluoride. I prefer to go without them, even though they may be good for me in certain conditions, just as I do without digitalis, and male fern, scammony and stramonium, pilocarpin and antipyrin in my daily food; and I have decided objections to having vested commercial interests regard my stomach in the light of a catch-basin of a pharmacy.

I am firmly convinced that there must be some real cause for the upward trend in the death rate from diseases of the kidney, beyond greater exactness in diagnosis. Doubtless, many deaths from kidney diseases were formerly returned as due to other causes; perhaps it would be fair to say that, until within comparatively recent years, mortality statistics in respect to kidney diseases have no great value; but recent returns show this upward trend, which is worthy of very serious consideration. Some would attribute it to alcohol; but is the general public any worse in its abuse of alcohol than formerly? Our ancestors drank spirits and strong wines in goodly amounts, and in

the early days of colonial times regarded water as a most undesirable beverage, and yet they were remarkable for their longevity. Some say that we live under a greater nervous strain than did our ancestors, but certainly they had many causes of anxiety that are unknown to us of later generations. True, they had nothing of the nervous strain that accompanies the modern desire to accumulate wealth, but we have not the constant fear of hostile acts of the aborigines, and do not need the companionship of a rifle on our way to church. We are better off in most ways than they were. We are better housed, better clothed, better looked after when sick, and better circumstanced generally; but are we better fed? In many ways, yes. We have food in greater variety, and it is better prepared. We have green vegetables the year round, while they had them only during the period of their growth. We have fruits and other supplies from long distances, which their primitive methods of transportation did not permit. But at least they were not forced to eat foods that were chemically preserved.

Unfortunately, we cannot test preservatives on man except for short periods; and even with "poison squads," we cannot observe what insidious changes may be going on in the structure of the various organs. To determine what tissue changes occur, we must have recourse to animal experimentation, and even then we cannot be sure of the correctness of analogic reasoning. But it is the best we can do; and if our experimental animals show degenerative changes, we must at least consider the possibility of harm to man.

Another objection which I have to chemical preservatives is the fact that, if they are effective, less care will be exercised in handling and preparing foods. A man aware of the fact that his lack of ordinary care and cleanliness will be set straight by the compound that he is using is likely to take advantage of it; and in order to make sure of his results he will throw in an extra amount.

In the matter of evidence concerning the effects of a preservative, we must bear in mind that we have two kinds of investigators: 1. Those who have no pecuniary interest in a verdict *pro* or *con*, and seek only the truth. 2. Those who have such an interest, and hence are biased from the start. Those who find adversely have nothing to gain by saying so. Their work and time count for nothing in the way of pecuniary reward; they give their time and pay the cost of their

researches; they publish their results and are abused by those whose ox is gored. Those of this class who find for or against a given preservative announce their results and are satisfied. They do not lash themselves into a fury at the crass ignorance shown by those who find otherwise, as do some of those who begin their work with a bias. Whenever I see a violent attack made on an adverse report, with abuse of the scientific knowledge of the one responsible therefor, and an appeal in behalf of the downtrodden merchant, I cannot help wondering what is behind it all. If we see a criticism of somebody's all-wool suits or guaranteed pure white-lead paints, we do not expect to see laboratory philanthropists taking up the matter and rushing to their defence, after giving liberally of their time and money, and abusing the critic. Why, then, is it the case with food preservatives? I know of a number of men in this country, in England, and in Germany, who have each put forth elaborate and expensive defences of certain food preservatives, and I know, also, that in most instances they are under pay. Recently I was attacked for some work which I had published concerning the effects of sodium sulphite. The expensively gotten-up pamphlet purported to come from a certain research laboratory, and the writer thereof showed an undue amount of tendency to special pleading. I wrote to a colleague in the same city asking information concerning the writer and the research laboratory, and found what I had supposed to be the case: that the writer was a manufacturer of food preservatives, and that his research laboratory was located within his factory. So it is well to look askance at some of the favorable evidence presented, for it may not be wholly frank and impartial.

Some advocate the unrestricted use of preservatives, provided the buyer is warned by a label of the presence and percentage of the agent used. While this is in a sense a move in the right direction, it must be said that, unless the customer is qualified to judge of the possibility of harmful results, such information is quite valueless.

Dr. C. B. Cochran: A generation ago nearly all articles of food were prepared for the table at home. Meats, vegetables, fruits of all kinds were dried, canned, pickled, or preserved by one process or another at home. Jellies, jams, marmalades, etc., were then home-made articles. Now the great bulk of all this work is taken from the home and is done in factories.

The greater part of these factory-made goods contain non-condimental, or chemical preservatives. In this State the preservative most in use to-day is benzoic acid.

The theory by which Dr. Vaughan explains the selective action of poisons may be applied to explain the action of certain food preservatives on different forms of plant and animal life. Formaldehyde, for example, is far more fatal to some forms of life than to others. It is probably true that plant life is more sensitive to its action than animal life. While the presence of 1 part of formaldehyde to 40,000 parts of water will kill or greatly retard the growth of lactic acid bacilli, such a solution can be borne by minnows and tadpoles for weeks at a time. Even paramecia appear to resist formaldehyde solutions of this strength for some time.

Similar statements can be made in regard to salicylic acid. Although this acid is not a violent poison to mammalian life, it is fatal to fish, even in very minute quantities. In its action upon fish, it is as quickly fatal as prussic acid is to mammals.

Another point is certainly of importance—that is, many preservatives unquestionably influence certain foods unfavorably as to digestibility, even though they do not evidently influence health directly. This is strikingly seen in connection with formaldehyde. 1 : 500 of this substance in milk absolutely prevents coagulation of the milk; 1 : 1000 retards coagulation greatly. These figures refer to the coincident addition of formaldehyde and rennet. If formaldehyde is added first and rennet only some time after, the effect is even more marked, and is seen in greater dilution; 1 : 2000 showing a marked effect. Formaldehyde also makes the curd very tough and hard. This is very graphically shown by the effect of sulphuric acid. With natural milk the curd from 10 c.c. is dissolved by about 6 c.c. of sulphuric acid; if 1 : 400 of formaldehyde is present in the milk, it takes about 36 c.c. of sulphuric acid to dissolve the curd. This influence on the curd can be seen with as little as 1 : 10,000 formaldehyde.

December 8, 1904.

A Cabinet for Investigating the Action of Vaporizable and Gaseous Disinfectants and Insecticides, and for Teaching Disinfection to Students.

By W. M. L. COPLIN, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

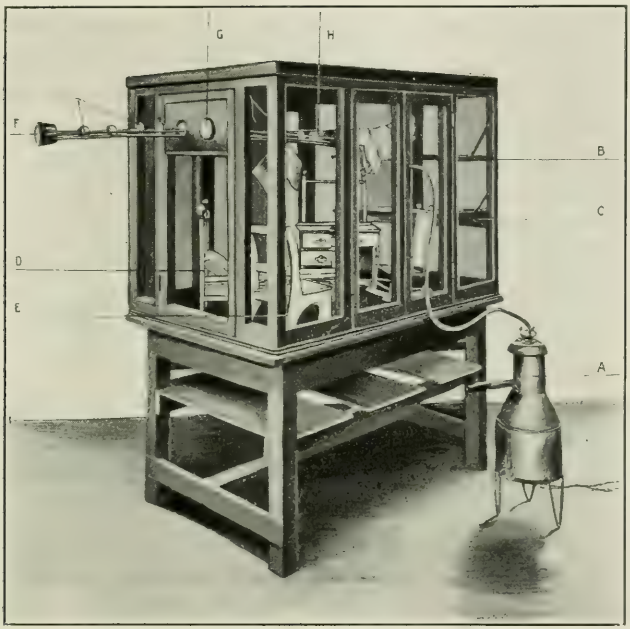
THIS cabinet is a rectangular compartment, 1 metre (40 inches)[1] wide, 1 metre (40 inches) in height, and 1.5 metres (60 inches) in length, constructed of wood and glass. The wood frame is of dressed yellow pine, 4 cm. ($1\frac{5}{8}$ inches) square, solidly framed together, and resting on a table 67 cm. (27 inches) in height. The glass is bedded in putty and secured in position by strips of wood; the bottom of the case, at its junction with the table, as well as the doors, is rendered as tight as possible by the use of rubber-edged weather strips. Upon one side are two doors, each 30 cm. (13 inches) wide and 90 cm. (36 inches) in height, hinged and closed so as to afford as accurate co-aptation as possible. One of these doors fastens on the inside with two bolts, the other closes and locks to the first, and is supplied with an ordinary door-knob of a kind usually applied to the doors of dwelling-houses, and, like them, removable for the introduction of the discharge tube from a formalin generator. At one end there is another door, which it was thought might be useful for the introduction and removal of anything after the connections with the formalin generator had been made by the device already indicated; it could have been omitted without imperilling the value of the device. The top of the case is also panelled and glazed, thereby fully lighting its interior; if for any reason it is desired to darken the case a light-proof rubber cloth is thrown over and around it.

At one end of the case is a flat shelf, 15 cm. (6 inches) in width, for the reception of Petri dishes, test solutions, etc. Just below this is a second shelf, inclined at such an angle that tubes containing bouillon may be laid upon it without spilling the fluid or moistening the cotton plugs which may be left in place. The interior of the cabinet is supplied with a complete set of doll's furniture, consisting of bed, mat-

[1] The metric equivalents in inches given in this article are approximate.

tress, pillows, the necessary linen, an ordinary chair, a rocking chair, and a bureau; the drawers and side compartment of the latter contain the trousseau necessary for a young lady of her social position.

In one end of the case, shown in the accompanying illustration, occupying the upper portion of the door, is a device for the introduc-



Cabinet in use: *A*, formalin generator, heated by electricity; *B*, flat shelf for test-objects; *C*, inclined shelf for fluid mediums; *D* and *E*, bed and chair of doll's chamber-suit, the bureau of which can be seen in the back part of the cabinet; *F*, device for the introduction and removal of test-objects, etc.; this tray is withdrawn; *G*, same as *F*, but pushed into the cabinet; the leader from the letter *G* is on the conical plug that closes the opening through which the tray moves; leader over letter *F*, test-objects in tray *F*, outside the cabinet; *H*, test-objects in tray *G*, inside the cabinet.

tion of test-objects and also for their removal during disinfection of the chamber. This device is made in duplicate, both parts being exactly alike. It consists of a board, 5 cm. (2 inches) in thickness, set in the upper part of the door, and perforated by two openings, each 7 cm. (3 inches) in diameter, through which passes a movable carrier, each end of which is supplied by a conical wooden plug that can be made

to engage in the circular opening, so as to secure a practically air-tight closure. This carrier is 60 cm. (24 inches) in length, and consists of five round, wooden rods, so set into the small ends of the plugs that together they form a tray in which can be deposited pill-boxes, small Petri dishes, and bottles or tubes, the diameters of which do not exceed that of the opening through which the carrier passes. When out and loaded, the carrier can be forced into position in a fraction of a second, or can be withdrawn from the interior in the same length of time. As both ends of the carrier terminate in conical plugs that tightly fit the opening, the latter is always closed, except during the brief interval necessary for pushing the carrier in or pulling it out. When pulled out the opening is closed by the inner plug, and when pushed in, by the outer plug. Were I reconstructing this device, I should so arrange it that one carrier would be at the upper and the other at the lower end of the door. The cabinet should be longer, certainly 2 metres (80 inches), and so constructed that it could be placed on end or flat to meet special indications. I do not recall any publication describing a similar device, but Dr. M. J. Rosenau, Director of the Hygienic Laboratory of the United States Marine Hospital and Public Health Service, has applied essentially the same principle to the wall of a small room in which experiments on disinfection are conducted; although we had used the disinfection chamber for several years, the device for securing removable test-objects was based on a rather imperfect recollection of Dr. Rosenau's apparatus.

For instructing the class in the principles of disinfection, the following steps are necessary: Two side doors are opened, giving free access to the interior; it is then explained that in actual practice, before entering the room, the individual having charge of the disinfection would put on a suit, consisting of impermeable overalls, jacket, and overshoes; that if a carpet were present, this would be raised, rolled, and placed in an impermeable bag for transportation to a steam-disinfecting plant in the city. As in many localities such facilities are not available, the carpet is then so suspended that it can be sprayed on both sides with formalin solution, and later exposed to the action of formalin vapor used for disinfecting the chamber. It is also explained that the mattress and pillows would be similarly treated. The drawers are removed and stood on edge and their contents, along

with the bed-clothing, suspended from a cord placed across the upper part of the chamber. Small openings are made in the mattress and a number of test-objects introduced; one pillow is suspended from the cord and the other, as shown in the illustration, is laid on top of the mattress, with test-objects interposed. Test-objects are also placed upon the shelves and in the carriers. The carpet is then sprayed with formalin solution, and it is explained to the class that the individual making the arrangements would now remove his impermeable suit and overshoes, step out of the room, close and lock the door, removing the knob, and introducing the nozzle of the formalin generator. The method of sealing windows and doors is now explained and illustrated. Around some of the openings, or part of one door, cotton or rag strips are forced into position by the use of a case-knife; other cracks around doors are closed by pasting over them strips of paper or, what is better, but more likely to injure highly polished surfaces, strips of rubber adhesive plaster. The formalin generator is now started and the test begun. At appropriate intervals (two to ten minutes) a test-object—either a pill-box or an open Petri dish—is removed from the carrier and given to the student who prepared the test-object. In this way fifty students may be permitted to participate in the experiment and observe the results of disinfection over long or short periods. On the following day the cabinet is opened, any test-objects in the interior are removed, and portions of the carpet or other bodies permeable with difficulty may be excised with sterile instruments and studied by cultural methods. It is possible to arrange on the carrier a container, so that samples of the mixed air and gas can be removed from time to time for percentage determinations. It is unnecessary to describe other methods that may be tested, as it is evident that any of the methods or appliances for disinfection of a room can be utilized and studied in similar ways; the apparatus readily yields itself to any method of fumigation.

The cabinet is also especially useful for the study of the insecticidal value of combined insecticides and disinfectants, or for the study of insecticides alone. Insects, such as mosquitoes, bed-bugs, roaches, flies, and also small animals, if desirable, can be placed in the chamber, and the action upon them of known volumes of the gas can be investigated. Of course, the glass sides are impermeable and the small

strips of intervening wood offer practically no opportunity for the escape of gas; percentage leaks can be arranged for by valves, imperfect seals, or the carrier can be left but partly closed. Flies and mosquitoes lodge upon the glass and can be watched with a lens, if necessary, or they may be introduced in cages upon the test-object-carriers, and are, therefore, removable after selected periods. The chemical action of disinfecting agents can, in a small way, be studied by the use of this cabinet. Especially well does it afford an opportunity for observing the bleaching action of chlorine compounds; test-paper saturated with dyes or special reagents may be suspended in the chamber as to show clearly by their reaction the lines along which diffusion of evolved gas follows.

The apparatus has been in use in the laboratories of the Jefferson Medical College Hospital for a number of years and has fulfilled our expectations. Where a number of men are moving about in a rather restricted space around the cabinet, a formalin generater heated by oil or alcohol might be upset and constitute a danger that is avoided by the use of a generator heated by electricity, as shown in the cut. The electrically heated generators are not satisfactory for the disinfection of large quarters, as those with which I am familiar do not afford sufficient heat to secure rapid volatilization of the formaldehyde solution in large quantities. *October* 27, 1904.

Supernumerary Anterior Extremities in a Frog.

By GUTHRIE McCONNELL, M.D.

The specimen is a small frog that was found in Rhode Island last September. It attracted attention from the fact that in the water it was seen to swim in circles. It was caught, and on examination was found to possess an extra pair of legs, projecting at right angles from a point immediately above the normally situated front leg. The normal leg was very much undersized, probably on account of the nutrition having been taken away to a great extent by the extra pair.

The extra legs articulate with a bony process that projects about an eighth of an inch from the body. Motion is well marked, and the legs are well developed.

It was first thought that the mass of bone which extends beyond the articulating surfaces was the posterior end of an incompletely formed spinal column. Examination, however, by a low-power lens revealed no anal opening, and the toes were seen to represent much more closely the conformation found in the anterior rather than that of the posterior extremities. An *x*-ray picture also showed a bone extending laterally from the vertebræ; one that gave no indication of segmentation.

Until a thorough examination had been made the case was thought to be one of *Dipygus parasiticus*, the partial formation of another individual. Such a condition results from the duplication of the anterior or posterior part of the primitive embryonal area and medullary groove, and from this the autosite is developed.

One point against this being a case of dipygus is that such a parasite is better developed in all cases in which it arises from some point high up the spinal column. Those coming from the neck may have a trunk and four limbs, while those arising low down usually possess lower extremities only.

Ordinarily the shoulder girdle consists of a pair of curved cartilages arising from several primitive segments, the dorsal surface of which becomes the spine of the scapula. This does not touch the spinal column. The limbs develop from little bud-like processes that arise from two lateral longitudinal ridges.

It has been experimentally shown in tadpoles that abnormalities will result from injuries during the early stages of development. The more advanced the stage of formation, the less severe will be the deformity. In this case the injury must have occurred at the time of the formation of the shoulder girdle. The original bud divided, and one part continued its normal development in a hypoplastic form. The second portion attempted the formation of a complete shoulder girdle with the two accompanying arms, in this way giving rise to the deformity described. *October* 27, 1904.

Erosive Gastritis.

By JOHN FUNKE, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

The fact that comparatively little work, both from a clinical and an experimental point of view, has been done upon this subject, makes it an interesting as well as important one, especially since it is claimed by some authorities to be the forerunner of gastric ulcer. As early as 1861 Rokitansky and later Rindfleisch and Key expressed the conviction that hemorrhagic gastric erosions may give rise to gastric ulcers. Langerhans, on the other hand, maintains that hemorrhagic erosions rarely become chronic ulcers of the stomach; and that erosions and gastric ulcers in their origin, in their site, and in their form have little in common. He comes to these conclusions from the fact that peptic ulcer is, as a rule, single or there are at most three or four, while erosions are usually multiple. Ulcers are commonly found at the pylorus and upon the lesser curvature, while erosions are principally situated upon the mucous folds; and when erosions are numerous they coalesce and form large branched figures, while the shape of an ulcer rarely changes except when two unite. Gerhardt is convinced that in one case he reports the erosions gave rise to ulcers; in the other two he is not certain whether the erosions are responsible for the ulcers. Einhorn believes the erosions are not forerunners of ulcers, because in none of his cases did an ulcer develop. I am inclined to take a broader view than even Langerhans and Einhorn, and regard peptic ulcer and erosions as in no way dependent upon each other. I do not believe that gastric ulcers always develop from erosions, for the latter are frequently associated with inflammatory conditions of mucous membrane in other parts of the alimentary canal. I further do not believe that the condition, "erosions of the gastric mucosa," is an entity, but that, as a rule, it occurs with other diseases of the mucous membrane of the stomach. Rosenberg describes a vesicular eruption upon the lips, the tongue, and the hard and soft palate, in which the covering of the vesicles is, for the most part, seen lying loose, generally in shreds, and in place of the vesicles there are easily bleeding and sharply outlined erosions. Osler says small and

superficial ulcers occur in chronic pharyngitis; he also says that abdominal operations, especially when injuries to the omentum occur, give rise to erosions of the stomach. Comby, in discussing athrepsia, asserts that minute superficial erosions and hemorrhagic effusions are found in the mucous membrane of the stomach, at the pylorus, and the greater curvatures. The peptic glands are destroyed and the sustaining connective tissue is increased. Nicholls notes that in simple catarrhal inflammation of the intestine slight erosions of the mucosa may occur. Of acute catarrhal gastritis, he says: "Here and there small hemorrhages and superficial erosions may be seen." White, in speaking of colitis, associated with pyemia and other septic conditions, maintains that the mucous membrane is thickened, rough, vascular, and covered with small ulcers and patches of yellow lymph. Hemmeter is inclined to the view that during adult life tiny exfoliations and erosions occur in all stomachs. When the erosions become extensive, it is because the resistance of the mucosa has been reduced by one of the forms of gastritis or by carcinoma.

Etiology. Virchow maintains that interference with the onward flow of the blood through the liver gives rise to dilatation of the veins and congestion of the mucosa of the stomach, which produces hemorrhagic necrosis and chronic ulcer; acute and chronic catarrh and conditions that excite violent vomiting and muscular contraction can in themselves give rise to hemorrhagic necrosis and ulcer. Rokitansky informs us that hemorrhagic erosions resulting from acute and chronic diseases and from injuries of various kinds, occur at all periods of life, even in infants. With the erosions, he says, hyperemia and hyperacidity of the gastric juice appear. Because of the hyperacidity, the gastric juice attacks the tissues and the bloodvessels, and hemorrhage results. The swelling of the mucous membrane accompanying the erosions is, according to Rokitansky, a concomitant of the hyperemia; from this, he says, it is evident why gastrorrhea predisposes to hemorrhagic erosions. Korczynski and Jaworski are of the opinion that changes in the nerve centres and changes in the vessels or anemia of the mucous membrane may predispose to loss of superficial structure, to ulcer, and to hemorrhage; but as causative factors there must be hyperacidity and increased digestive powers of the stomach. They further state that, with a deficiency of hydrochloric acid, bleeding gastric ulcer

cannot occur. Klebs notes hemorrhage from the intestinal tract incident to muscular contraction consecutive to extensive burns of the skin. At post-mortem he found many erosions following the folds of the duodenum. Hardtung believes erosions arise principally through muscular contraction; blood in the mucosa being unable to return, it is forced into the tissue, and this cuts off the circulation and autodigestion takes place. The clinical histories of the two cases he reports show violent vomiting in one and violent colic in the other; in the latter the bleeding was from the duodenum. Pitt maintains that erosions of the gastric mucosa following extensive burns of the legs do not extend deeply and present no thickening around them, but are not developed post-mortem. Langerhans believes diseases of the bloodvessels, such as aneurysm and emboli, are rarely the cause of hemorrhagic erosions, while chronic catarrh and contractions of the gastric musculature are frequent causes. In most of Einhorn's cases a chronic gastritis was associated with the erosions. Einhorn thinks the gastritis gave rise to the erosions, but, he adds, there may be some unknown factors that enter into the etiology. In six of the seven cases he reported there was a decrease in the hydrochloric acid; in the seventh it was increased. Einhorn believes anemia and chlorosis are secondary to erosions. Decker, by introducing hot foods into the stomachs of two dogs, produced hemorrhagic erosions in one and typical ulcer in the other. Dreschfeld says that after injuries and disease of the central nervous system hemorrhagic erosions of the stomach develop, but it is doubtful if they always lead to the formation of ulcers. Dreschfeld believes that the acute ulcers that follow burns of the skin are produced by changes in the blood. By injecting staphylococci into the stomach he produced gastric erosions and ulcers. Nauwerck concludes that certain hemorrhagic erosions are due to peptic solution of the mucosa after hemorrhagic infiltration; few result from mycotic necrosis. Letulle saw gastric ulcer develop in a man suffering from dysentery; the bacteria isolated from the stools, when injected into guinea-pigs, gave rise to erosions and ulcers of the stomach. In another instance he saw gastric ulcer develop in guinea-pigs after the injection of streptococci derived from the blood of a puerperal woman. According to Letulle's view, these ulcers may arise in two ways: 1. If bacteria find a nidus on the mucosa of

the stomach the ulceration may proceed from this point. 2. The ulceration may follow embolism and necrosis of the mucous membrane. Hemmeter inclines to the view that primary necrosis is caused by bacteria; later the necrotic areas undergo digestion. He says bacteria can exist in the cells and in and around the floors of the ulcers, notwithstanding the high acidity of the gastric juice. He found erosions in the stomachs examined one hour after death, and in which autodigestion was prevented by filling the organ with alcohol. Dieulafoy is convinced that erosions are due to rapid and limited necrosis of a small part of the mucosa, with no inflammation or at most an insignificant reaction. In his case, he regards the erosions as due to the pneumococcemia from which the patient died. Pneumococci were found along the borders as well as in the erosions. Gerhardt asserts that there are two essential points in the production of gastric ulcers: 1. A local reduction in the resistance of the mucous membrane. 2. A digestion of this area. The latter may be due to an excess of hydrochloric acid or to reduced alkalinity of the blood. Riegel says the mucosa of a drunkard's stomach is frequently covered with erosions. L. Müller produced hemorrhagic erosions and ulcers of the gastric mucous membrane of dogs by artificial occlusion of the portal vein or some of the larger gastric branches. Talma, by ligating the esophageal and pyloric orifices in rabbits, succeeded in producing hemorrhagic erosions and typical ulcers. R. de le Vedora incised the vagus and then injected absolute alcohol into the ends of the nerve; the celiac and splanchnic plexuses were injected with absolute alcohol. No changes resulted from his experiments on the vagus, but from those on the celiac plexus erosions and necrosis of the gastric mucosa occurred in 5 out of 12 cases, while, as a result of the injuries to the splanchnic plexus, similar changes were found in 9 out of 15 cases. The lesions were in the usual site of gastric ulcer and were accompanied by hyperchlorhydria. Pariser maintains that chlorosis plays an important part in the etiology of gastric erosions. Fenwick believes that syphilis, by inducing endarteritis and cutting off the blood supply, gives rise to inflammatory thickening of the mucosa, interstitial hemorrhage, and superficial ulceration. Swan is convinced that syphilis produces erosions, ulcers, and tumors of the stomach. Bendict maintains that the type of ulcers of the stomach

most nearly related to the ordinary skin ulcer consists of erosions found in acute toxemias and traumatic gastritis. He also speaks of hemorrhagic erosions due to back pressure of the blood commonly seen in chronic gastritis and dependent upon hepatic cirrhosis. Dufour, in speaking of infectious hematemesis occurring in purulent infections, surgical septicemias, and in obscure forms of blood poisoning, asserts that the lesion in the stomach is either a simple ecchymosis of the mucosa or a perforating ulcer—Dieulafoy's "ulceratio simplex." Glockner reports a case in which there were hemorrhagic erosions, gastritis, and peptic ulcer of the cardia and lower portion of the esophagus. He notes considerable extravasation of blood into the floors of the erosions; in the vessels of the tunica propria and submucosa he found mixed thrombi, which induced him to view the erosions and ulcers as primarily due to the thrombi and secondarily the result of autodigestion of the infarcted area.

In discussing simple colitis, White states that we do not know the cause of this condition, and that neither occupation, place, nor previous disease, except nephritis, seems to have any relationship to it. Bleeding is common in these cases, sometimes in traces, sometimes in large quantities. White maintains that there is never any satisfactory gross or histologic evidence that the condition begins in the solitary follicles. He believes that severe inflammations lead to necrosis of the mucous membrane which is exfoliated in the form of small particles or sloughs. White further asserts that vascular ulceration may be due to atheroma. In considering the cause of gastritis, Nicholls maintains that, in the majority of instances, the condition is due to irritating substances, some of which may be circulating in the blood; many foods act as irritants, particularly when the functions of the stomach are impaired, as, for instance, by fibrosis, cancer, pyloric stenosis, or muscular atony.

The condition, in my opinion, is analogous to ulcerative stomatitis and ulcerative colitis, not including with the latter that form due to inflammation and swelling of the solitary follicles. The erosions result from superficial necrosis, and are not necessarily due to the action of the gastric juice. I do not doubt that embolism and thrombosis of the vessels of the stomach occur and that the areas of infarction undergo autodigestion, but I believe the condition is infrequent,

and that the majority of erosions are due to other causes. It is a pretty well established fact that the stomach suffers secondarily as a result of many diseases. Then, again, many substances are secreted into the stomach which may produce deleterious effects upon its mucosa; for instance, Hare is responsible for the statement that when in the body morphine is changed into oxydimorphine, the latter is eliminated into the stomach and is there reabsorbed, and then induces secondary changes. If this substance is capable of inducing changes after absorption, it is reasonable to suppose that it is capable of producing alterations of the mucous membrane after it is absorbed; and if the stomach eliminates oxydimorphine, it is also possible that other noxious materials are secreted into the organ. Taking into consideration these facts, and also the clinical and anatomic observation that erosions frequently accompany gastritis, I must conclude that hemorrhagic erosions are, in many instances, simply part of the already existing gastritis; on the other hand, I am convinced that in some cases the condition is dependent upon some poisonous material in either the food or in the blood, or it results from the introduction of virulent bacteria into the stomach.

It was thought unnecessary to include in the following report a description of any organs other than the stomach, since the latter alone is interesting. The pathologic diagnosis is as follows: Fibroid myocarditis, fibrocalcareous tuberculosis of the lungs, chronic splenic capsulitis, chronic parenchymatous nephritis, and gastritis, with erosions of the mucosa.

Stomach. Along the lesser curvature, for some distance toward the cardia, around the pylorus, and for a short distance upon the greater curvature, but near the pylorus, are many small, depressed areas, varying from 1 mm. to 1 cm. in diameter. In the majority of instances they are circumscribed and isolated, although every now and then two are seen which have coalesced. These areas are round, oval, or irregular in outline; the edges are bevelled, sometimes presenting deep indentations; a few are rounded and slightly elevated. In a few areas the edges are not so well defined, but appear to merge imperceptibly into the surrounding mucosa; the depth of the erosions varies from 1 mm. to 2.5 mm.; the floors are smooth and pale. The depth does not seem to depend upon the size of the area, as some of the deepest

are but 0.3 cm. in diameter. Few of the areas are situated upon the folds of the mucous membrane, the greater number being between them. The intervening mucous membrane is pale and slightly edematous.

Small blocks of the stomach wall were fixed in Bensley's fluid, dehydrated in alcohol, and embedded in paraffin. Sections were made and stained with hematoxylin-eosin, by Van Gieson's method for connective tissue, by Weigert's method for elastica, by Mallory's reticulum stain, by Gram's for bacteria, and with polychrome methylene blue, and methylene blue.

Histology. The mucosa is not uniform in thickness; here and there are wide gaps which vary in depth and breadth. In a number of sections the gaps or erosions extend through one-half the depth of the mucosa, while in others they reach almost to the muscularis mucosæ. From the margin of the erosion the surface inclines gradually to the centre, from which point it again gradually ascends to the other margin. Upon one erosion lies a necrotic mass not completely separated from the mucosa. It is made up of necrotic tissue containing many cellular elements, principally lymphoid in type, although a few epithelial-like cells are present; there are, however, no recognizable tubules in the mass. Overlying all the erosions is a layer of necrotic tissue, which is fairly uniform in thickness and contains more lymphoid cells than the mass just described; there are also present a number of oat-shaped nucleated cells in this necrotic layer. Few tubules extend as far as the necrotic layer; as a rule, a belt of cellular tissue intervenes. The tubules in many places run parallel, but every now and then they are tortuous and the tortuosity is more marked near the eroded surface. The lining ephithelium is of the columnar type; the basal-placed nuclei are oval, stain faintly, and the chromatin granules are fine and scanty. Many of the epithelial cells show mitotic figures. The lumina of the tubules contain degenerated cells and a delicately reticulated substance, which is tinged a deep lavender with Mallory's reticulum stain. Where the erosions have reached almost to the muscularis mucosæ the tubules in the centre of the lesion are destroyed.

The interstitial tissue is made up of delicate strands of fibrous reticulum, which is abundantly infiltrated with lymphoid cells, a few

red blood cells, and a number of polymorphonuclear leukocytes. The vessels are distended with blood.

I am convinced that the cellular infiltration and the distention of the bloodvessels are indicative of an inflammatory reaction.

The erosions are also found upon the rugæ, but they are not confined to these situations, nor are all the rugæ involved. The mucosa of the stomach between the eroded areas reveals changes indicative of a chronic catarrhal inflammation, which, for the most part, is limited to the superficial portion of the mucous membrane. In the non-eroded portions the tubules are more regular in their arrangement and the epithelium less degenerated.

We were unable to find bacteria in either the erosions or the inflamed mucous membrane.

Many of the vessels in the muscular and peritoneal coat show conspicuous changes. The intima is not uniform in thickness; at points it presents a nodular condition, while in other vessels the thickening involves nearly one-half of the inner circumference. In the peritoneal coat the intima of the vessels is uniform in thickness. The internal elastica in many vessels is separated into two layers for some distance, but these layers finally unite and then continue as one layer throughout the remainder of the course. In other vessels this layer is irregular and distorted, and its waves are larger than normal. The media in many of the larger vessels is thickened; the elastica and fibrous tissue of this coat stand out prominently. The external elastica is, upon the whole, little changed.

Diagnosis. Chronic catarrhal gastritis, with extensive erosions.

I do not believe that the arteriosclerosis bears any etiologic relations to the erosions in this case. The arterial disease is, in my opinion, a part of the general process.

In regard to the morbid anatomy and the histology, Rokitansky says that at times hemorrhagic erosions of the gastric mucosa are few in number, but they may involve the entire pyloric half of the stomach. The mucous membrane is swollen and covered with grayish mucus. The hemorrhage, even with a few small erosions, is often considerable. Lying upon the denuded areas, he finds detritus, epithelium from the tubules and parts of formed tubules containing degenerated granular masses, the whole being impregnated with brown pigment.

The tubules in the bases of the erosions contain a great deal of pigment. Langerhans says the erosions measure about 6 mm. in diameter; they are round, the edges are wavy and ragged, and the floors are smooth and gray in color. In discussing the histology of erosions, Gerhardt calls attention to the fact that the floor is made up of the deeper parts of the mucosa, in which the tubules show an irregular arrangement, are slightly curved, and do not always run parallel. The vessels in the floor show no change. Hemmeter asserts that the erosions include the inner third of the gland ducts proper; he notes that before the necrotic portion is dislodged the process of repair has already begun in the underlying tissue. The epithelium of the tubules in the mucous membrane adjoining the erosions shows mitotic figures. The lesion is in the vicinity of the sphincter antri pylorici about 7 cm. from the pylorus. Dieulafoy notes that the erosions are sometimes round, sometimes oval; they measure 2 cm. to 3 cm. in diameter, and exist all over the surface of the gastric mucosa, but principally at the pylorus. Near and at the base of the erosion there is clear evidence of an inflammatory reaction. *November* 10, 1904.

Proceedings

of the

Pathological Society of Philadelphia.

New Series, Vol. VIII. No. 2, 1905

TABLE OF CONTENTS.

McFarland, On the Occurrence of a Fibrinolytic Ferment in the Blood Serum.—Pearson and Gilliland, The Effect of Tuberculosis Vaccinations upon Cattle Infected with Tuberculosis.—Longcope, A Study of the Bone-marrow in Typhoid Fever and Other Acute Infections.

On the Occurrence of a Fibrinolytic Ferment in the Blood Serum.

By JOSEPH McFARLAND, M.D.

Certain morbid conditions, of which croupous pneumonia may be taken as a type, are characterized by exudations of which fibrin is an essential component. Fibrin as known to us is a product of the coagulation of the blood, is an absolutely insoluble, extremely stable, resisting proteid substance, so that it becomes difficult for us to account for its ready removal from the tissues during convalescence from disease. This is particularly true of pneumonia, in which the air cells of the lung are filled with coagulated exudate containing an abundance of fibrin. As a rule, this fibrin disappears rapidly after the crisis of the disease and during the period of convalescence, but in exceptional cases this does not take place until so long a time has elapsed that new fibroconnective tissue forms upon and replaces it. Why this difference should occur does not seem to have been determined. It would appear to depend upon the existence of some fibrin-dissolving enzyme in the blood. Should this be the case, it would seem as if the resolution of pneumonia might be assisted in ordinary cases, and brought about in those unfavorable cases in which it is delayed by the use of artificially prepared serum contain-

ing this enzyme. It might even be that such an enzyme containing serum might be capable of preventing the formation of fibrin in the exudate in pneumonia, in which case the disease should not be more serious than in acute œdema of the lung.

To determine the existence of such an enzyme in the blood serum, and to prepare artificially a serum that might contain it, are both matters fraught with considerable technical difficulty. I performed the following experiments with the hope of determining that a fibrinolytic serum could be produced experimentally:

The Preparation of a Standard Fibrin. For this purpose the blood of a normal horse was permitted to coagulate, the buffy coats from the coagula removed from the red corpuscular mass below, and washed for twenty-four hours in clean running water. The resulting white solid masses were then cut into small fragments, and again washed in running water. They were then finely minced, and the remaining serum they contained as carefully as possible removed by pressing through a cloth. The minute fragments of fibrin were then spread out in a porcelain dish and rapidly dried. This procedure yielded a large number of translucent, glue-like fragments, which were ground to a fine powder and passed through the finest grade of chemical sieve, so as to have the particles as homogeneous as possible. This powder, which consisted of almost perfectly pure fibrin, was utilized in all of the experiments.

My first endeavors to produce the fibrinolytic serum were made in the Pasteur Institute in Paris during the summer of 1903. The pulverized fibrin, in the proportion of 1 gram in 5 c.c. of physiologic salt solution, was injected beneath the skin of the abdominal wall. These experiments were without success—in the first place, because a number of the animals used became infected, the preparation not being sterile, and because rabbits and guinea-pigs, not becoming infected, seemed unable to dissolve the fibrin, which remained beneath the skin, forming a hard induration.

Prof. Metchnikoff, with whom I conferred in regard to the experiment, suggested that I prepare a fibrin that would be sterile, or that I experiment with some animal not easily infected, and also added that in the event of failure to achieve either of these I should continue to experiment with fibrin from other animals than the horse, the horse's

fibrin possibly being more difficult of solution than fibrin from the guinea-pig, the rabbit, or from man.

Returning from Paris, I continued the experiment in my own laboratory, using dogs for the purpose. These animals never became infected and seemed well able to dissolve the horse's fibrin. After each injection a swelling remained for about forty-eight hours and then rapidly disappeared, so that by the fourth day nothing abnormal could be determined at the seat of inoculation. This encouraged me to believe that if the animals were compelled to dispose of the fibrin frequently enough, their serum might eventually become rich in the fibrin-dissolving substance, whatever it might be, and with this hope in view I continued to administer the fibrin suspension at infrequent intervals, as shown by the following memoranda: November 13, 1903, 1 gram; 24th, 1 gram; December 9th, 1 gram; 24th, 1 gram; January 16, 1904, 1 gram; February 3d, 1 gram; 10th, 1 gram; 27th, 1 gram; March 15th, 1 gram; 30th, 1 gram; April 5th, 1 gram.

On March 1st blood was drawn from a small fox-terrier dog that had been thus treated, and also from a control dog that had received no fibrin. To 2 c.c. of the clear serum of each dog 1 gram of the fibrin powder was added, and the tubes of the serum stood in the incubator. At the end of five hours no change was observed in the fibrin powder, which remained as a granular sediment of equal bulk in both tubes. I concluded that the serum had no fibrinolytic power.

On May 13th the dog was bled again, as was also a control dog that had received no fibrin, and to 2 c.c. of the blood of each animal 1 gram of the fibrin powder was added. These tubes were stood in the incubator and examined carefully every hour. At the end of eight hours no change could be observed. At the end of twenty-four hours signs of bacterial contamination appeared in the serum of the control dog, but still, in both tubes the fibrin powder remained as a granular precipitate in equal bulk, and when shaken diffused itself throughout the fluid. At the end of forty-eight hours signs of bacterial contamination were evident in both tubes, yet the fibrin powder seemed to be unaltered in either, appearing as the same granular precipitate in equal bulk in both tubes, and still disseminating itself in the same way throughout the fluid when the tubes were shaken. From this I am led to infer that the disappearance of the fibrin powder in the

treated dog depended upon some more complicated mechanism than the presence of a fibrinolytic enzyme in the serum of the blood.

The experiment is open to the very important criticism that bacteria were not excluded, that the powder itself, according to the method of preparation, was not sterile, and that the serum to which the powder was subsequently added became unavoidably contaminated from it, but this does not militate against the results obtained, since the dog receiving the fibrin powder did not become infected, and since the bacterial infection of the serum did not in any way affect the fibrin, which remained as an insoluble precipitate in both tubes.

Discussion.

Dr. Leo Loeb: Under various conditions enzymes which are not the ordinary digestive enzymes can almost undoubtedly dissolve fibrin. Possibly Dr. McFarland injected, besides the fibrin, something that produced an antibody. Was there any appearance of precipitation; that is, any clouding when the serum of the injected animal was added to the fibrin?

Dr. McFarland: There was no appearance of coagulating action, and certainly little active substance besides fibrin could have been left after the clots had been many times washed. Also the fibrin did not go into solution, but was in suspension, so that coagulation could not occur. *October* 27, 1904.

The Effect of Tuberculosis Vaccinations upon Cattle Infected with Tuberculosis.

By LEONARD PEARSON, B.S., V.M.D.,

AND

S. H. GILLILAND, V.M.D., M.D.

During recent years a large amount of work has been done by Koch, Trudeau, de Schweinitz, von Behring, Maragliano, Fraenkel, and others for the purpose of discovering and developing a specific treatment for tuberculosis. This work has taken various directions, and has included experiments wherein the toxins of tubercle bacilli have been administered, and experiments wherein antitoxins found

in the blood of animals that have been treated with toxins have been used. Toxins of various kinds have been employed; from the original and new tuberculins of Koch to the toxalbumin, the watery tuberculin, and the degreased tubercle bacilli of Maragliano, and bacillary pulp.

The antitoxins that have been used have been developed as a result of the injection of the various toxins mentioned above, and also living tubercle bacilli of low virulence.

The reports of the therapeutic experiments made upon infected animals with tuberculosis toxins and antitoxins are numerous, but cannot be regarded as convincing. Most of these experiments have been on rabbits and guinea-pigs. Neither rabbits nor guinea-pigs are altogether satisfactory for experiments of this kind; the former because of their comparative immunity to tubercle bacilli of the human type, the latter on account of their excessive vulnerability to inoculation tuberculosis of either of the mammalian types. Enough work has been done to denote that the progress of a tuberculous infection may be controlled in some degree by specific means. It is important that these various methods shall be compared and measured, both quantitatively and qualitatively. There is here a large and important field of labor for the critical experimentalist.

Among the means that have been proposed for controlling the spread of tuberculosis among cattle is vaccination, or the inoculation of animals with living cultures of tubercle bacilli of low virulence for the animals into which they are inoculated. This method of producing artificial immunity has been the object of considerable study, both in this country and in Europe, and has been reported upon to this Society by the writers of this paper.

In connection with some tuberculosis vaccination experiments made by the writers, the opportunity occurred to test the effect of vaccination upon some young cattle already infected with tuberculosis. As this treatment appears to have had a decided effect upon the course of the disease in the infected animals treated, it is considered that our observations should be placed upon record, especially since the work covered nearly two years, long enough to show definite results, and is the first of the sort of which we have knowledge.

In testing with tuberculin in a large herd of Shorthorn and grade

Shorthorn cattle in December, 1902, that was known to have been infected with tuberculosis for a number of years, it was found that practically all of the members of the herd responded affirmatively to the test. Among the animals so responding were twelve calves from six to eight months old. As these calves had mingled rather freely with the members of the herd, and as they had been reared on the milk of extensively tuberculous cows, it was not surprising to find that they responded to the tuberculin test. These twelve calves were obtained for use in this experiment. They were shipped to Philadelphia and were placed in a temporary building on the grounds of the veterinary school, where they were kept apart from other cattle.

The twelve calves were again tested with tuberculin February 2 and 3, 1903. All responded to this test. They were then weighed and divided into two lots of six each, as nearly equal as possible in respect to age, size, weight, and condition. One of these lots was subdivided into two groups of three each.

The three calves of one of the subgroups were given seven intravenous injections of a standard suspension[1] in water of tubercle bacilli of human type (Culture M). The dosage began at 1 c.c. and was increased to 6 c.c. The intervals between injections were from six to twenty days, and the period covered was from February 9 to May 1, 1903, as is shown by the protocols. These same calves received another and final intravenous injection of 5 c.c. of a standard suspension of living tubercle bacilli (Culture M) about a year later, March 29, 1904.

The three calves of the second subgroup were given subcutaneous injections of tuberculin at intervals of from two to ten days. The injections of tuberculin were repeated until the hypersensitiveness of the animals to tuberculin had disappeared, after which the calves received an intravenous injection of a suspension of tubercle bacilli (Culture M) in water. Following each intravenous injection of living tubercle bacilli, the animals were again given tuberculin a number

[1] By a standard suspension is here meant a suspension of tubercle bacilli in water in such quantity as to give an opacity equal to that of a twenty-four-hour culture of typhoid bacilli in bouillon. 1 c.c. of such a suspension is estimated to contain the equivalent of 0.0013 gram of tubercle bacilli dried ten days in a desiccating chamber over calcium chloride.

of times until the hypersensitiveness to tuberculin again disappeared. The procedure in these cases in respect to the order of the injections of tuberculin and tubercle bacilli was as follows: Two subcutaneous injections of tuberculin, an intravenous injection of tubercle bacilli; six injections of tuberculin, an injection of tubercle bacilli; six injections of tuberculin, an injection of tubercle bacilli; three injections of tuberculin. The period of treatment extended from February 9 to April 30, 1903, inclusive; the exact times of administration and the doses are shown by the protocols. The calves of this group, as of the first group described, were given an intravenous injection of 5 c.c. of standard suspension of living tubercle bacilli (Culture M) March 29, 1904. Following this, tuberculin was administered five times at intervals of three or four days.

The remaining six calves were given no treatment whatever, but were, at all times, kept with the six calves under treatment, so that all of the twelve calves in this experiment were subjected to the same conditions and subsisted upon the same kind and quantity of food.

All the calves were kept in a stable until May 29, 1903, when they were placed upon pasture, which became very scanty during the latter part of the season. During the winter of 1903–04 the cattle were fed mixed hay, corn-fodder, and a grain mixture of bran and corn-meal. Only a little grain was fed. About the middle of May, 1904, the cattle (now about two years old) were again placed on pasture, where they remained until they were killed at the close of the experiment.

Two cattle, both controls, died: the first one, May 5, 1903; the second, September 13, 1904. Two, one control and one treated, were killed April 4, 1904, and the rest were killed in September, 1904.

When the cattle in this experiment died or were killed, they were submitted to careful postmortem examination. Material was stained for examination for tubercle bacilli, and guinea-pigs were inoculated from the lesions of some of them. Histologic examination of the lesions were made by Dr. C. Y. White, to whom we are greatly indebted for reports upon his examinations.

The treatments and postmortems are summarized in the following protocols.

First Group. Three calves that received intravenous injections of tubercle bacilli alone.

I.—*Red Bull* (16,013).

1902.	December	19.	0.1 c.c. tuberculin; reaction.
1903.	February	2.	0.8 c.c. " " to 106.2°.
"	"	9.	0.0013 grm. human tubercle bacilli, intravenously.
"	"	18.	0.0032 " " " " "
"	March	2.	0.0039 " " " " "
"	"	21.	0.0039 " " " " "
"	April	4.	0.0052 " " " " "
"	"	10.	0.0065 " " " " "
"	May	1.	0.0078 " " " " "
1904.	March	29.	0.0065 " " " " "
"	September	15.	Killed.

Necropsy. Weight, 643 pounds; fair condition. The lesions of tuberculosis found in this animal are as follows: At the lower border of the middle lobe of the right lung was a slightly depressed area, about one-half inch in diameter, containing a collection of thick, yellow pus, filling a cavity the size of a large pea. The walls of this cavity are one-eighth of an inch thick, white, and of firm, dense texture. In one of the left peribronchial glands there is a caseocalcareous nodule, about the size of a pea and having the appearance of a wholly closed process. Guinea-pigs inoculated from the lesion in the lung became tuberculous.

II.—*Red and White Bull* (16,017).

1902.	December	19.	0.1 c.c. tuberculin; reaction.
1903.	February	2.	0.8 c.c. " " to 105.6 F.
"	"	9.	0.0013 grm. human tubercle bacilli, intravenously.
"	"	18.	0.00325 " " " " "
"	March	2.	0.0026 " " " " "
"	"	21.	0.0039 " " " " "
"	April	4.	0.0052 " " " " "
"	"	10.	0.0065 " " " " "
"	May	1.	0.0078 " " " " "
1904.	March	29.	0.0065 " " " " "
"	September	15.	Killed.

Necropsy. Weight, 467 pounds; good condition. The following lesions of tuberculosis were found: In one of the left peribronchial glands a yellow caseous area, one-tenth of an inch in diameter. In the posterior mediastinal gland there is an area, the size of a pea, yellow

in color, and quite calcareous, surrounded by a white, dense capsule. In the middle mediastinal gland there is a similar area, though much smaller, being but one-twelfth of an inch in diameter. In one of the postpharyngeal glands there is a caseocalcareous area, one-half of an inch in diameter, surrounded by an unusually thick, dense, white, fibrous wall. The caseous collection contains many calcareous grains. There are also in this gland three other similar areas, much smaller, about one-eighth of an inch in diameter, and each is surrounded by a dense capsule. In addition to this evidence of tuberculosis, it is observed that both lungs, although generally well inflated, are heavy, soggy, somewhat leathery, and without elasticity. There are some small areas where the tissues are contracted and dense. Histologically, these areas show numerous dense bands of connective tissue. The bloodvessels are very much thickened. In limited areas, some of the smaller ones are almost obliterated. Some of the smaller sublobules show the lung tissue to be collapsed or organized. The peribronchial lymphatic tissue is increased, and the pleura is thickened. There is no caseation or evidence of a tuberculous process, excepting as above noted. Guinea-pigs inoculated with the caseocalcareous material from the thoroughly encapsulated lesions in the postpharyngeal glands became tuberculous.

III.—*Roan Heifer* (16,021).

1902. December	19.	0.1 c.c. tuberculin; reaction.
1903. February	2.	0.8 c.c. " " to 106° F.
" "	9.	0.0013 grm. human tubercle bacilli, intravenously.
" "	18.	0.0026 " " " " "
" March	2.	0.0026 " " " " "
" "	21.	0.0039 " " " " "
" April	4.	0.0052 " " " " "
" "	10.	0.0052 " " " " "
" May	1.	0.0065 " " " " "
1904. March	29.	0.0065 " " " " "
" September	15.	Killed.

Necropsy. Weight, 465 pounds; good condition. The evidence of tuberculosis here consists in a very dense condition of the lower half of the posterior flap of the anterior lobe of the left lung, which is attached to the posterior lobe and to the pericardium and the diaphragm. This dense mass consists of a very thick wall of fibrous tissue surrounding a sequestrum of lung tissue, about one and one-

half inches in its anteroposterior, and two and one-half inches in its vertical diameter. Above this mass the lung tissue of the anterior lobe contains an excessive quantity of fibrous tissue appearing as white bands between the lobules. These bands are quite firm and are from one-eighth to one-quarter of an inch wide. The parenchyma surrounded by these bands is studded with fine dots and lines of white, that consist of fibrous tissue. Above this sclerotic zone the lung tissue is elastic and pink. There are nowhere nodules or caseous areas, excepting in one of the left peribronchial glands, which contains a caseocalcareous nodule, the size of a pea.

There is reason to believe that in this animal there has been an extensive area of tuberculous tissue in the lower portion of the anterior lobe of the left lung. This area appears to have become encysted, and the lung tissue above to have been the seat of numerous small tubercles, which were transformed into scar tissue and appear now very much hardened and contracted.

Second Group. Three calves which received intravenous injections of tubercle bacilli alternating with repeated subcutaneous injections of tuberculin.

IV.—*Red and White Heifer* (16,015).

1902.	December	19.	0.1 c.c.	tuberculin; reaction.	
1903.	February	2.	0.8 c.c.	" "	to 105.8° F.
"	"	9.	1.0 c.c.	" "	to 102.8° F.
"	"	15.	1.5 c.c.	" "	to 103.0° F.
"	"	18.	0.0026 grm.	human tubercle bacilli,	intravenously.
"	"	22.	1.0 c.c.	tuberculin; reaction	to 103.0° F.
"	"	24.	1.5 c.c.	" "	to 102.6° F.
"	March	4.	2.0 c.c.	" "	to 104.6° F.
"	"	6.	2.5 c.c.	" "	to 102.8° F.
"	"	11.	3.0 c.c.	" "	to 103.0° F.
"	"	14.	3.5 c.c.	" "	to 103.0° F.
"	"	21.	0.0039 grm.	human tubercle bacilli,	intravenously.
"	"	27.	1.0 c.c.	tuberculin; reaction	to 103.2° F.
"	"	29.	1.5 c.c.	" "	to 103.0° F.
"	April	5.	2.0 c.c.	" "	to 102.6° F.
"	"	8.	2.5 c.c.	" "	to 102.2° F.
"	"	10.	3.0 c.c.	" "	to 104.0° F.
"	"	16.	3.5 c.c.	" "	to 103.6° F.
"	"	18.	0.0052 grm.	human tubercle bacilli,	intravenously.
"	"	23.	05 c.c.	tuberculin; reaction	to 104.6° F.
"	"	27.	1.0 c.c.	" "	to 102.6° F.
"	"	30.	2.0 c.c.	" "	to 103.6° F.

1904.	March	29.	0.0065 grm. human tubercle bacilli, intravenously.		
"	April	1.	1.0 c.c.	tuberculin;	reaction to 102.8° F.
"	"	4.	2.0 c.c.	"	" to 103.3° F.
"	"	8.	3.0 c.c.	"	" to 102.4° F.
"	"	11.	4.0 c.c.	"	" to 102.9° F.
"	"	15.	5.0 c.c.	"	" to 103.8° F.
"	September	15.	Killed.		

Necropsy. Weight, 566 pounds; good condition. The only evidence of tuberculosis in this animal is a calcareous nodule, one-eighth of an inch in diameter, situated in one of the left peribronchial glands. This nodule is sharply differentiated from the surrounding adjacent, quite normal, glandular tissue, and has the appearance of a completely closed process. Guinea-pigs inoculated with an emulsion of this nodule developed tuberculosis.

V.—*Red and White Heifer* (16,019).

1902.	December	19.	0.1 c.c.	tuberculin;	reaction.
1903.	February	2.	0.8 c.c.	"	" to 105.6° F.
"	"	9.	1.0 c.c.	"	" to 103.4° F.
"	"	15.	1.5 c.c.	"	" to 102.8° F.
"	"	18.	0.0026 grm. human tubercle bacilli, intravenously.		
"	"	22.	1.0 c.c.	tuberculin;	reaction to 104.0° F.
"	"	24.	1.5 c.c.	"	" to 103.8° F.
"	March	4.	2.0 c.c.	"	" to 103.8° F.
"	"	6.	2.5 c.c.	"	" to 103.2° F.
"	"	11.	3.0 c.c.	"	" to 104.2° F.
"	"	14.	3.5 c.c.	"	" to 103.8° F.
"	"	21.	0.0039 grm. human tubercle bacilli, intravenously.		
"	"	27.	1.0 c.c.	tuberculin;	reaction to 104.6° F.
"	"	29.	1.5 c.c.	"	" to 102.6° F.
"	April	5.	2.0 c.c.	"	" to 102 8° F.
"	"	8.	2.5 c.c.	"	" to 103.2° F.
"	"	10.	3.0 c.c.	"	" to 102.6° F.
"	"	16.	3.5 c.c.	"	" to 103.0° F.
"	"	18.	0.0052 grm. human tubercle bacilli, intravenously.		
"	"	23.	0.5 c.c.	tuberculin;	reaction to 102.8° F.
"	"	27.	1.0 c.c.	"	" to 102.4° F.
"	"	30.	2.00 c.c.	"	" to 103.8° F.
1904.	March	29.	0.0065 grm. human tubercle bacilli, intravenously.		
"	April	1.	1.0 c.c.	tuberculin;	reaction to 102.9° F.
"	"	4.	2.0 c.c.	"	" to 103.0° F.
"	"	8.	3.0 c.c.	"	" to 103.0° F.
"	"	11.	4.0 c.c.	"	" to 103.8° F.
"	"	15.	5.0 c.c.	"	" to 102.4° F.
"	September	15.	Killed.		

Necropsy. Weight, 580 pounds; good condition. One of the left peribronchial glands contains two nodules, each about one-tenth of an inch in diameter. Both are distinctly calcareous and are sharply differentiated from the immediate adjacent, quite normal, gland tissue.

The right lung is rather dense and leathery and contains some collapsed areas. In a collopsed area there is found an infiltration of round cells surrounding the bronchial walls. The lymphatic nodes in the same region are greatly increased. The alveoli are edematous, and in some places the exudate has undergone organization.

There is no evidence of caseation or of tuberculosis.

VI.—*Red Heifer* (16,022).

1902.	December	19.	0.1 c.c.	tuberculin;	reaction.
1903.	February	2.	0.8 c.c.	"	" to 105.2° F.
"	"	9.	1.0 c.c.	"	" to 103.0° F.
"	"	15.	1.5 c.c.	"	" to 104.4° F.
"	"	18.	0.0013 grm. human tubercle bacilli, intravenously.		
"	"	22.	1.0 c.c.	tuberculin;	reaction to 103.2° F.
"	"	24.	1.5 c.c.	"	" to 104.0° F.
"	March	4.	2.0 c.c.	"	" to 105.6° F.
"	"	6.	2.5 c.c.	"	" to 103.8° F.
"	"	11.	3.0 c.c.	"	" to 103.2° F.
"	"	14.	3.5 c.c.	"	" to 104.0° F.
"	"	21.	0.0039 grm. human tubercle bacilli, intravenously.		
"	"	27.	1.0 c.c.	tuberculin;	reaction to 103.4° F.
"	"	29.	1.5 c.c.	"	" to 102.8° F.
"	April	5.	2.0 c.c.	"	" to 102.6° F.
"	"	8.	2.5 c.c.	"	" to 102.8° F.
"	"	10.	3.0 c.c.	"	" to 103.2° F.
"	"	16.	3.5 c.c.	"	" to 103.4° F.
"	"	18.	0.0039 grm. human tubercle bacilli, intravenously.		
"	"	23.	0.5 c.c.	tuberculin;	reaction to 103.6° F.
"	"	27.	1.0 c.c.	"	" to 102.2° F.
"	"	30.	2.0 c.c.	"	" to 104.2° F.
1904.	March	29.	0.0065 grm. human tubercle bacilli, intravenously.		
"	April	1.	1.0 c.c.	tuberculin;	reaction to 103.0° F.
"	"	4.	2.0 c.c.	"	" to 103.3° F.
"	"	8.	3.0 c.c.	"	" to 103.8° F.
"	"	11.	4.0 c.c.	"	" to 103.1° F.
"	"	15.	5.0 c.c.	"	" to 102.2° F.
"	"	30.	Killed.		

Necropsy. Weight, 421 pounds; unthrifty condition. The only distinct evidence of tuberculosis in this animal is a calcareous nodule,

the size of a pea, in the left bronchial gland. The pleura and peritoneum are more or less opaque and show films or flakes of fibrin partly or wholly organized, and in some places evidently of considerable age. Guinea-pigs inoculated from the calcareous nodule in the bronchial gland became tuberculous.

It is evident that this animal had suffered with a widespread inflammation of the serous membranes, from which it practically recovered. Such a diffuse inflammation of the serous membranes of both visceral cavities occurs in tuberculosis of cattle of the type of pearl disease. But in this case there were no tubercles or evidence of tuberculosis. One must consider the possibility that in this animal there was a healed, fresh tuberculosis of the pleura and peritoneum.

Third Group. Six calves which received no treatment and were kept as controls for the purpose of comparison.

VII.—*Red and White Bull* (16,014).

1902. December 19. 0.1 c.c. tuberculin; reaction.
1903. February 2. 0.8 c.c. " " to 105.6° F
" May 4. Died.

Necropsy. Weight, 430 pounds. This bull died suddenly, apparently of acute indigestion. The only evidence of tuberculosis in this animal consists in the presence of caseous nodules, as large as a pea, in both bronchial and in the mediastinal lymphatic glands.

FIGURE VIII.—*Red and White Heifer* (16,016).

1902. December 19. 0.1 c.c. tuberculin; reaction.
1903. February 2. 0.8 c.c. " " to 106.0° F.
1904. September 17. Killed.

Necropsy. Weight, 578 pounds; poor condition. In the left lung, at the bottom of the posterior lobe, there is an area containing numerous tubercles, some of which have undergone caseation. Two similar areas are found in the tip of the lung. The surrounding lung tissue is red and dense and is infiltrated with small gray tubercles of pinhead size, some of which have cheesy centres. The posterior mediastinal gland is five inches long and two inches in diameter. This gland is filled with dense nodules, most of which have undergone caseation, and some of which contain calcareous deposits. Guinea-pigs inoculated with infiltrated lung tissue developed tuberculosis.

IX.—*Red and White Heifer* (16,018).

1902. December 19. 0.1 c.c. tuberculin; reaction.
1903. February 2. 0.8 c.c. " " to 106.4° F.
1904. September 19. Killed.

Necropsy. Weight, 415 pounds; poor condition. Both the anterior and middle lobes of the right lung are attached to the chest-wall; the anterior lobe is also attached to the pericardium. There are numerous tuberculous areas of all ages and up to one and one-half inches in diameter scattered rather thickly through both lungs. Both the bronchial and the mediastinal glands are enlarged and contain numerous caseous and caseocalcareous nodules.

X.—*Red and White Bull* (16,020).

1902. December 19. 0.1 c.c. tuberculin; reaction.
1903. February 2. 0.8 c.c. " " to 105° F.
1904. September 13. Died.

Necropsy. Weight, 480 pounds; fair condition. This bull was apparently quite healthy on September 12th, and was found dead in the stable the next day. It was found that there was a great collection of gas in the paunch, and this appears to have been the cause of death, through interference with respiration by pressure upon the diaphragm. The evidence of tuberculosis in this animal consisted in the presence of several caseous nodules in both bronchial glands; the posterior mediastinal gland is six inches long and quite thick. The entire structure of this gland has undergone degeneration. Both postpharyngeal lymphatic glands are slightly enlarged and contain caseous areas.

It is quite possible that in this case the enlarged mediastinal lymphatic gland was a contributing cause of death through pressing upon the esophagus and tending to interfere with the regurgitation of gas.

XI.—*Red and White Heifer* (16,023).

1902. December 19. 0.1 c.c. tuberculin; reaction.
1903. February 2. 0.8 c.c. " " to 106.4° F.
1904. April 30. Killed.

Necropsy. Weight, 313 pounds; very poor condition. This heifer was killed because it was in such bad condition that it could not live long.

The costal pleura of both sides are coated with masses of round and

flattened nodules occurring singly and in patches. The largest patch is nearly a foot in diameter and about two inches thick. Both lungs are covered with round and flattened nodules, some of which are closely attached to the pleura and some of which hang from the pleura singly and in clusters. There is a fringe around the borders of the lungs about two inches wide and very thickly studded with hard nodules, the centres of which have undergone caseation. Both lungs contain a large number of caseous areas. The bronchial and mediastinal lymphatic glands are considerably enlarged and caseous. The postpharyngeal glands are in similar condition. The omentum, the walls of the stomach, the abdominal walls, the spleen and liver are coated with nodular masses that are characteristic of pearl disease. There are numerous caseous areas in the substance of the liver. The bronchial lymphatic glands are enlarged to several times their natural size, and are caseous.

This is a case of "pearl disease," in the most advanced form and of widest distribution.

XII.—*Red and White Bull* (16,024).

1902. December 19. 0.1 c.c. tuberculin; reaction.
1903. February 2. 0.8 c.c. " " to 106° F.
1904. September 17. Killed.

Necropsy. Weight, 524 pounds; good condition. The right bronchial gland is somewhat enlarged and contains a calcareous nodule. In the anterior lobe of the right lung there are numerous nodules containing pus. These are surrounded by firm, fibrous walls. The intervening lung tissue is collapsed.

The observations here recorded show a decided difference between the lot of six young cattle that were treated and the six that were not treated. Since the two lots of animals were in all respects as nearly equal as possible at the beginning of the experiment, and since they were cared for all together and in precisely the same way, excepting in respect to specific treatment, it is but fair to conclude that the six treated animals were favorably influenced by the treatment.

We believe that we have sufficient evidence to justify the statement that the treatment to which six of the animals were subjected had the effect not only of keeping in check the progress of the tuberculous

process, but in causing a distinct and in some cases (Nos. II., III., and VI.) a great retrogression of the lesions. In other words, the treatment had a distinct curative effect.

In all of the treated animals the lesions were quiescent and encapsulated. But they contained living tubercle bacilli. There is room for difference of opinion as to whether an animal, or a person, in which there is a tuberculous lesion containing living bacilli may be regarded as cured. If the lesion is wholly cut off by a thick fibrous wall from living tissue, and if it is incapable of again becoming active, it would appear that a claim for a cure might fairly be entered. But how is one to know that activity may not be re-established? If there is resistance enough to cause the complete encapsulation of *all* tuberculous lesions in the body it is evidence that a considerable degree of immunity has been developed. If the bacilli in the lesions are of such low virulence that they cannot infect an animal of the species of the one in which they are found, renewed activity is not to be expected. de Schweinitz found living tubercle bacilli in minute nodules in the lungs of a cow inoculated intravenously a year before with bacilli of human type that appeared to have been incapable of producing progressive disease. Nodules may occur from intravenous injections of dead tubercle bacilli. Fraenkel and von Behring have found in lesions of tuberculosis of cattle, tubercle bacilli that are not pathogenic for cattle.

Unfortunately, in these experiments, the virulence for cattle of the tubercle bacilli in the lesions in the treated animals was not determined.

These experiments, which were made on a few young cattle in the earlier stage of the tuberculosis, do not justify conclusions or inferences as to the probable effect of similar treatment on older and more extensively diseased animals. Experiment must be made on a larger and broader scale. We have at this time a number of animals under treatment which we hope will give us more knowledge on this subject.

But we hold that the experiments that have been made show clearly that under such treatment as was given, tuberculous lesions do not extend; on the contrary, that they recede, and that new implantations do not occur, even upon prolonged contact with tuberculous herd mates.

Discussion.

Dr. Eshner asked whether the animals treated with bacilli and tuberculin show any better results than animals that are treated with tuberculin alone.

Dr. Alburger noted that all the lesions in the diagram seemed, with one exception, to be on the left side in the treated animals. He asked whether there is any reason for this?

Dr. Pearson replied that he used tuberculin in 1892 in treating tuberculous cows, and some of these animals did distinctly better than controls. Some of them, however, ran the usual course and appeared to be uninfluenced by the tuberculin. He had never tried it in calves; and in calves it would be especially important, as the disease more frequently runs a rapid course in them. The situation of the lesions on one side in the animals treated with bacilli and tuberculin cannot be explained; it is comparable to the fact that a horse with beginning glanders usually shows the earliest lesion in the left nostril.

December 22, 1904.

A Study of the Bone-marrow in Typhoid Fever and Other Acute Infections.

By WARFIELD T. LONGCOPE, M.D.

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The close relationship that has been shown, especially by Ehrlich,[1] to exist between certain cells of the hemopoietic organs and the cells of the circulating blood renders a study of the bone-marrow, lymph glands, and spleen in acute infectious diseases of special interest. The blood changes in typhoid fever are characterized particularly by a decrease in the total number of white cells, and in this respect the disease differs essentially from pneumonia and many other acute infections where an increase of leukocytes is the rule. It was therefore thought that a comparative study of the bone-marrow in typhoid fever and other acute infections, combined with a study of the leukocytes of the circulating blood in these conditions, might be of some value.

In the literature upon the histology of typhoid fever few references

are made to the microscopic appearance of the bone-marrow. It is true, that Ponfick,[2] in 1872, noted the presence of large red blood-carrying cells in typhoid bone-marrows, and considered them analogous to the phagocytes in the spleen and lymph glands; and Mallory,[3] in his well-known study upon the histology of typhoid fever, describes the changes in the bone-marrow from two cases. The lesions were similar to those found in the spleen. Large endothelioid cells filled the blood and lymph spaces, while foci of necrosis were scattered through the blood-forming tissue. Lymphoid cells and polynuclear leukocytes were present. Within the last year Fraenkel[4] has called particular attention to the focal necroses of the bone-marrow in typhoid fever. He found these foci of necrosis present in thirteen cases, but besides this lesion, which he considers specific, he describes the presence of hemorrhages, accumulations of small round cells, and diffuse degenerations which he believes may occur in conditions other than typhoid. In the bone-marrow from all thirteen cases he could demonstrate typhoid bacilli by cultures, and in this statement he substantiates Quincke,[5] who found typhoid bacilli in the marrow of eight out of nine cases of typhoid fever.

Although Fraenkel states that focal necroses of the bone-marrow are not known to occur in diphtheria, scarlet fever, erysipelas, pneumonia, or peritonitis, he says that the lesions do occur in the bone-marrow from cases of variola. Chiari[6] first emphasized these lesions in variola and termed the condition "osteomyelitis variolosa." Councilman, Magrath, and Brinckerhoff[7] have given a very careful description of the changes in the bone-marrow in twenty-seven cases of variola. They note particularly the absence of polymorphonuclear leukocytes and the relative increase of large basophilic cells and premyelocytes. Extensive degeneration, both in definite foci and a diffuse degeneration affecting single cells, was found in many cases, while the abundance of large phagocytic cells sometimes enclosing fat, sometimes filled with marrow cells, together with their focal accumulations, seemed to be characteristic of the disease. The large phagocytic cells are believed to be of endothelial origin.

In the present study bone-marrow was examined in twenty-six cases of typhoid fever, and for comparison in fifteen cases of pneumonia, four of peritonitis, two of miliary tuberculosis, one of acute

cerebrospinal meningitis, one of retroperitoneal abscess, one of puerperal septicemia, four of chronic nephritis, one of carcinoma of the gall-bladder, and of two normal individuals. In most instances the marrow from the upper third of the femur was studied, both in sections and in smear preparations. The normal marrow was obtained from the lower end of the tibia. In each instance the leg had been amputated immediately after an accident, before which the individual had been in excellent health. One patient was about thirteen, the other about twenty-three years of age. The tissues were hardened in Zenker's fluid. For staining methods hematoxylin and eosin, eosin and polychrome methylene blue, eosin-aurantia-toluidin blue, and Weigert's fibrin stain were found especially useful. The smear preparations were stained in most cases by Jenner's mixture. Ehrlich's triacid stain and other methods were occasionally employed.

During life the condition and numbers of the leukocytes in these cases were studied as far as was possible. An attempt was made to procure at least several leukocyte counts from all cases, the period of observation extending over several days before death. In many instances differential counts of the leukocytes were obtained.

Aside from the study of the structure of the bone-marrow, the cell differentiation is an extremely important point. By means of various stains it was possible to recognize in the sections as well as in smear preparations, aside from the nucleated and non-nucleated red blood corpuscles, cells belonging to different groups. To designate these groups the following terms will be used:

(*a*) Granular Cells. Neutrophilic granular myelocyte, a rather large cell, but usually varying somewhat in size, containing a round or oval, palely staining nucleus, poor in chromatin, and presenting a cytoplasm filled with small granules taking a pinkish or violet stain in polychrome methylene blue and eosin.

Eosinophilic granular myelocytes, cells similar to the neutrophilic variety, except that the granules are larger and stain bright red in eosin.

Certain transitional forms which contain either type of granule, but have an indented or slightly irregular nucleus.

Neutrophilic polymorphonuclear leukocytes.

Eosinophilic polymorphonuclear leukocytes.

Basophilic cells, with oval or irregular nucleus and protoplasm filled with large granules staining deep blue in methylene blue.

(*b*) Non-granular Cells. Large lymphocytes; large round cells about the size of a granular myelocyte, with large round nucleus rather rich in chromatin, surrounded by a narrow rim of protoplasm taking a definite basophilic stain.

Small lymphocytes, cells indistinguishable morphologically from the small lymphocyte of the lymph node.

Between the last two groups, however, many border-line cells were seen; cells somewhat larger than the small lymphocyte with slightly richer protoplasm; and, indeed, between the large lymphocyte and the granular myelocyte there were also elements which could not with surety be placed in either group. In general morphology these resembled the large lymphocyte except that the protoplasm contained a few definite neutrophilic granules.

In all of these twenty-six cases of typhoid fever the changes in the bone-marrow were the same in kind, though slightly different in degree. Congestion, edema, focal necrosis, and the presence of many large phagocytic cells was typical. A mild general hyperplasia of all the blood-forming cells, with always some and often a very decided relative increase of the non-granular cells and swelling of the lymphoid follicles, was a striking feature. There was usually a marked paucity of eosinophiles. In the uncomplicated cases polymorphonuclear leukocytes were abundant; in the cases complicated by acute infections those cells were much less numerous or practically absent. In those cases where the disease had lasted for three or four weeks the above lesions were more pronounced and the lymphoid hyperplasia was more marked than in the cases dying early in the attack. Where perforation and general peritonitis were the causes of death the congestion, edema, phagocytosis, and lymphoid hyperplasia were often extremely pronounced, while, besides the disseminated foci of necrosis, degeneration of single cells was noticeable. The marrow from cases dying of pneumonia, on the other hand, showed a greater hyperplasia of the blood-forming cells than was seen in any of the other groups. This hyperplasia sometimes resulted in the formation of almost a solid marrow, the granular myelocytes and lymphocytes occurring in about equal proportions.

The marrows from the cases of pneumonia, peritonitis not due to typhoid perforation, acute cerebrospinal meningitis, retroperitoneal abscess, and puerperal septicemia, presented quite a different appearance. In all of these conditions the qualitative changes were much the same, though there were differences in the grade of hyperplasia of the blood-forming cells. Sections showed, as a rule, congestion, but little edema. The hyperplasia of the cells varied from small, irregular, dense patches between the fat cells to a marrow which was practically solid and contained almost no fat. The type of cell which predominated was the granular myelocyte. These cells, together with the transitional forms, were present in enormous numbers, and at first sight often seemed to form alone the cellular patches. Mitotic figures were frequently observed. Polymorphonuclear leukocytes were distinctly rare. Eosinophiles were seen in moderate numbers. The lymphoid cells were notably scarce. Few small lymphocytes could be seen, while large lymphocytes, though not common, were sometimes encountered in small clumps. Lymphoid follicles were observed in only one or two sections. No foci of necrosis, such as those found in the typhoid marrows, could be discovered, and the large phagocytic cells, so characteristic of the lesions in the latter disease, were practically absent. Multinucleated giant cells were usually present in good numbers, and varying qualities of nucleated red blood cells were present.

Finally the marrows from the cases of nephritis and the tissue from the case of carcinoma of the gall-bladder correspond very nearly with the two normal marrows.

If we compare the appearance of the typhoid bone-marrows with the marrows from the cases of pneumonia, peritonitis, and the other acute infections we find changes which are constant and sufficiently distinctive to separate the two groups; for since the lesions in the cases of pneumonia, peritonitis, meningitis, etc., are of the same character, this group may be considered as one type standing over against the cases of typhoid fever, which show lesions of an entirely different nature. A third group may be made to include the marrows from the first three cases of nephritis and the cases of carcinoma of the gall-bladder, a group in which the histologic picture does not seem to differ essentially from the two normal marrows.

BONE-MARROW.

No.	Age.	Disease.	Duration in days.	Leukocytes.	Day of disease.	Complications.	Gross appearance.	Differential counts.							Normoblasts in 1000 white cells.	Megaloblasts.
								Granular myelocytes.	Polymorphonuclear leukocytes.	Small lymphocytes.	Large lymphocytes	Large mononuclear.	Basophiles.	Unidentified.		
1	28	Typhoid.	26	5,500 10,500	11th 25th	.....	Mottled red and yellow; very little cancellated bone.	46.6%	3.6%	34.2%	14.0%	0.4%	...	1.2%		
2	34	Typhoid.	w'ks	3,600	death	....	Grayish-red, soft; very little fat.	49.4	10.0	30.5	6.0	1.2	0.5%	2.4		
3	31	Typhoid.	10	4,000 4,500	6th 8th	.....	Mottled red and yellow; good deal of fat.	52.2	10.4	31.0	1.4	...	0.1	4.9		
4	18	Typhoid.	25	7,300	10th	Double acute fibrinous pleurisy; miliary abscess of lung.	Red, edematous, and soft; very little fat.	50.5	6.1	32.5	2.6	0.2	0.1	8.0	102	9
5	30	Typhoid.	50	4,600 5,400 5,500 3,700	31st 44th 45th 48th	Small abscess of prostate.	Mottled red and yellow, soft and edematous.	50.8	7.6	30.8	2.4	0.6	0.4	7.4	59	7
6	24	Typhoid.	33	5,000	15th	Tonsillitis and otitis media.	.....	42.3	2.6	44.4	4.5	0.2	0.2	5.8	18	0
7	50	Typhoid.	14	5,300 7,200 2,900	7th 13th 14th	Perforation on 13th day.	Mottled red, yellow, and gray; quite soft.	51.8	6.7	35.1	2.0	0.4	...	4.0		
8	?	Typhoid.	...	. ....	.....	Perforation.	.....	46.6	0.9	42.9	6.4	...	0.4	3.9		
9	19	Typhoid.	?	.....	.....	Perforation.	Soft; mottled red and yellow.	36.6	10.5	45.1	2.6	0.4	0.2	4.6		
10	?	Typhoid.	...	.....	.....	Lobar pneumonia.	.....	35.2	3.3	50.1	5.0	0.3	...	6.1	187	8
11	22	Lobar pneumonia.	10	34,900 24,300 54,000 55,000	6th 8th 9th 10th	.....	Mottled red and yellow; some cancellated bone.	67.2	7.4	13.4	11.2	...	...	0.8		

12	42	Lobar pneumonia.	6	36,200	4th	.....	Mottled red and yellow; soft.	65.8	1.8	20.8	6.2	0.4	...	0.5	15	0
13	40	Lobar pneumonia.	4	8,300	3d	.....	Mottled red and yellow; much cancellated bone.	67.5	2.3	19.5	5.3	...	0.1	5.3	22	3
14	44	Lobar pneumonia.	?	.....	.....	.....	Soft; mottled red and yellow.	64.0	2.5	22.3	7.0	...	...	4.2	92	7
15	20	Lobar pneumonia.	20	11,600 8,500 32,200	10th 14th 16th	.....	Mottled red and yellow.	67.2	3.2	13.3	7.5	0.1	...	8.7	118	15
16	38	Terminal pneumonia.	?	.....	.....	.....	....	75.3	4.3	14.3	3.8	0.2	...	2.2	9	1
17	?	Pneumonia unresolved.	...	.....	.....	....	.....	74.1	2.2	16.6	3.3	...	0.3	3.5		
18	21	Lobar pneumonia.	8	5,700	5th	.....	Mottled red and yellow.	72.5	0.9	20.0	2.9	0.1	0.1	3.5	11	0
19	28	Duodenal ulcer.	5?	21,000	5th	Perforation; peritonitis.	Mottled red and yellow, with a good deal of fat and cancellated bone.	62.8	12.3	14.7	9.4	0.8				
20	30	Duodenal ulcer.	2	.....	.....	Perforation; peritonitis.	Soft and red about periphery, but fatty toward central part.	60.5	3.5	22.5	10.0	0.5				
21	44	Duodenal ulcer.	20	18,000 11,900 50,500 42,500 42,500 54,500 38,500	6th 7th [illegible]th [illegible]th [illegible]th [illegible]th 26th	Perforation; peritonitis.	Soft and deep red throughout.	62.6	5.6	17.2	8.0	0.4	...	6.2		
22	31	Chronic nephritis.	7	.....	.....	.....	Fatty with a few red patches.	61.8	8.2	22.0	6.8	...	0.2			
23	31	Uremia.	5	.....	.....	.....	Mottled red and gray.	55.2	11.0	24.2	8.8	0.8				
24	22	Uremia.	?	.....	.....	.....	Fatty and yellow almost throughout.	56.6	4.8	31.2	1.8	0.8	...	4.8		
25	26	Chronic nephritis.	?	8,200	33d	.....	.....	50.8	25.7	12.8	5.0	0.6	0.3	4.7	10	1

The results of twenty-five differential counts of the bone-marrow cells are given in the accompanying table. Owing to the changes in the bone-marrow cells after death it was difficult to obtain perfect smear preparations, and, even when this was accomplished, to procure satisfactory stains. Therefore, many preparations were discarded as being unfit for a trustworthy count. Even in the best preparations broken or poorly stained cells were frequently seen, so that the percentages of the different types of cells are only approximately correct. In every instance the proportions were deduced from the count of a thousand cells, and as a rough index and control to the sections they seem of interest.

It would appear, then, that while in typhoid fever the hyperplasia is mainly of a lymphoid character, in the acute infections that are attended by a peripheral hyperleukocytosis the hyperplasia consists especially in an increase of the granular myelocytes. Doubtless in both conditions there is a general hyperplasia of all the cellular elements, and in the one instance the increase of the lymphoid series of cells and in the other the increase of the granular series is only relative. The results obtained from these differential counts do not bear out the work of Schurr and Löwy.[8] These authors examined the bone-marrow from cases of tuberculosis, cirrhosis of the liver, phosphorus poisoning, heart disease, typhoid fever, sepsis, pneumonia, and nephritis, but could find no relationship between the cell contents of the marrow and the leukocytes of the circulating blood.

The histogenesis of the bone-marrow cells has been much discussed of late, and, without entering too deeply into this subject, some knowledge of the matter must be gained before considering the bearing which the above findings may have upon the quantitative and qualitative changes in the leukocytes of the peripheral circulation. It is now fairly well established, especially through the work of Arnold,[9] Pappenheim,[10] Hirschfeld,[11] Walz,[12] Naegeli,[13] Wolff,[14] Michaelis,[15] and others that the bone-marrow is in part a lymphoid organ. Whether, as Pappenheim and Hirschfeld believe, certain members of the non-granular mononuclear series are true lymphocytes in the sense which Ehrlich considers them, and are identical with the lymphocytes of the lymph glands, or whether they are pecu-

liar to the bone-marrow and represent, as Naegeli, Wolff, and Rubinstein[16] claim, an indifferent cell in the process of development, cannot here be discussed. Dominici[17] has described accumulations of small lymphocytes in the bone-marrow of animals, and considers these structures analogous to the Malpighian bodies of the spleen. After inoculations of typhoid bacilli he has observed a hyperplasia of these lymphoid follicles.

Although the origin and destination of the small lymphocyte of the bone-marrow is as yet unsettled, there is a general uniformity of opinion that the large lymphoid cell or large lymphocyte is the forerunner of the granular myelocyte. It is also well established that the granular myelocyte may reproduce by indirect division.

The recent studies in lymphatic leukemia have thrown much light upon the histogenesis of the leukoblastic tissues. That the bone-marrow in certain forms of lymphatic leukemia may undergo a lymphoid hyperplasia is now well established, for since the earlier cases described by Michaelis, Wolff, Walz, Pappenheim, and Reed[18] many others have been reported to confirm the findings of these investigators. In this connection the studies of Flexner[19] and Bunting[20] upon myelotoxins and lymphotoxins are of much interest. These authors found that although the action of lymphotoxic sera when injected into animals was directed principally toward the lymph glands, still it produced a distinct increase in the lymphoid cells of the bone-marrows, and in their conclusion the authors regard the bone-marrow as a true lymphoid organ.

Professor Welch,[21] in his Huxley lecture, suggested that in typhoid fever the typhoid bacillus produces within the body a toxin which in main part gives rise to the lesions of the lymph glands, spleen, and lymphoid follicles of the intestines so typical of the disease. If then the bone-marrow is to be considered at least in part as a lymphoid organ it would not be surprising if in typhoid fever this structure should show changes analogous to the lesions in the other lymphoid organs. From a study of the above twenty-six cases it seems probable that the alterations of the bone-marrow in typhoid fever are essentially the same as those in the lymph glands, spleen, and lymphoid follicles of the intestines.

In order to appreciate the connection which may exist between

these lesions of the bone-marrow and the leukopenia of typhoid fever, it is necessary to consider first the changes in the bone-marrow of the second group and their relationship to the cells of the circulating blood. Although it is difficult to approach the question of hypoleukocytosis experimentally, the subject of hyperleukocytosis has been studied in this manner. Muir[22] found that for one to five hours after intraperitoneal injections of streptococci in animals the circulating blood showed a decrease in the number of leukocytes, followed by a marked increase dependent particularly upon the elevation of the amphophile leukocytes. The changes in the bone-marrow consisted first in a depletion of polymorphonuclear amphophiles, and later in a hyperplasia of the amphophilic myelocytes. Karyokinetic figures were frequently observed in these cells. Experimenting along these same lines, Rubinstein[16] has obtained similar results. After injecting rabbits with substances which produced a hyperleukocytosis he found an immediate withdrawal of the polymorphonuclear leukocytes from the bone-marrow. This was accompanied by an increase of the large lymphocytes, and followed later by a marked hyperplasia of the granular myelocytes. Brinckerhoff and Tyzzer,[23] by injecting hot salt solution into the peritoneal cavity of rabbits, have confirmed Rubinstein's work. Bunting[20] has perhaps carried the question still farther. Immediately after mild injections of myelotoxic sera in rabbits he obtained slight degenerative changes in the bone-marrow accompanied by a depletion of amphophile leukocytes and moderate peripheral hypoleukocytosis. The slight injury to the hemopoietic cells was rapidly followed by evidences of regeneration of the marrow cells with overproduction of the amphophile leukocytes. Together with this hyperplasia there was an elevation of the amphophile leukocytes of the circulating blood. If large doses of the myelotoxic serum were used the result was a destruction of the leukoblastic tissue of the bone-marrow, after which repair was difficult or impossible.

Without approaching the delicacy of an experimental investigation a study of the bone-marrow in the second group of acute infections, that accompanied by a hyperleukocytosis, and a comparison of the cells of the bone-marrow with the cells in the circulating blood, would lead one to the same conclusion as the above authors have

drawn regarding the correlation of these elements. In general the hyperplasia of the leukoblastic tissue of the bone-marrow was directly related to the height and duration of the peripheral leukocytosis. On the other hand, the relative increase of granular myelocytes varied but little; that is, in certain cases of pneumonia, where the numbers of leukocytes in the peripheral circulation were scarcely above the normal, the percentage of granular myelocytes in the bone-marrow was very high. This hyperplasia of the granular myelocyte seemed therefore to be essentially dependent upon the type of bacterial infection. The paucity of polymorphonuclear leukocytes was always striking. If one compares the differential counts of the marrow cells in many of these cases with the counts which Rubinstein gives for some of his animals that showed prolonged hyperleukocytosis, one is struck with the close correspondence of the two.

Certain variations from the above were noted. In two cases of pneumonia, where the leukocyte count during life was below normal, the bone-marrow at autopsy was almost entirely fatty, while in two other cases it showed red mottling. In one case where the leukocyte count was high, the marrow presented few cellular patches. In all of these instances the relative proportion of granular myelocytes was high, and polymorphonuclear leukocytes were rare or almost absent. It is possible that in the first two instances the functional activity of the marrow cells was exhausted. A like explanation may be offered for the third case.

Contrasting with the hyperplasia of the granular cells in the above group of infections, we have the hyperplasia of the non-granular cells in the typhoid group. The histology of the blood in typhoid fever has been thoroughly studied by Naegeli,[24] Thayer,[25] and many other observers, and we have quite accurate information as to the changes in the white and red cells which take place during the course of the disease. The striking feature is a marked decrease in the total number of white cells, with a diminution in the number of polymorphonuclear leukocytes and an increase in the number of lymphocytes. The large form of lymphocytes may be especially numerous. The eosinophiles are greatly diminished or absent. This leukopenia is usually noticeable by the second week, and in uncomplicated cases persists through the attack into convalescence. With the onset of

complications due to a secondary infection there may be a hyperleukocytosis with elevation of the polymorphonuclear leukocytes, but frequently the rise of white cells is not so great as in the same infection occurring as a primary condition and not as a complication of typhoid fever. Quite recently Kast and Gütig[26] have called especial attention to this point. They studied forty cases of typhoid fever complicated by secondary infections. In 80 per cent. of the cases the leukocytes remained below 7000. Especially is this true of perforation with general peritonitis. While many observers have emphasized the transient hyperleukocytosis that may occur at the onset of perforation, this phenomenon is not always observed, and, indeed, the elevation of leukocytes may be so slight and of such short duration as to be entirely overlooked; or, again, there may be a progressive decrease in the number of white cells. From a study of the blood counts made upon cases of perforation in typhoid fever at the Pennsylvania Hospital, Dr. Scott[27] finds the latter condition of great frequency, and emphasizes this lack of hyperleukocytosis.

The cause of the hypoleukocytosis in typhoid fever is not thoroughly understood. Many views have been advanced to explain the condition of hypoleukocytosis in general, but perhaps the most noteworthy of these is Ehrlich's theory of negative chemotaxis. Recently Naegeli[24] has put forth another view. He found a decrease in the granular cells and a proportionate increase in the non-granular cells of the bone-marrow in typhoid fever, and considered that these latter cells which he terms myeloblasts, and which he believes are the precursors of the granular myelocytes, are diverted from their normal function. He explains the hypoleukocytosis on the assumption that the typhoid toxin inhibits the production of myelocytes. But he views this as a cessation of the normal function and not as a destruction of the myeloblasts, since under certain conditions the marrow is capable of myeloid reaction as a response to the stimulus of a secondary non-typhoidal bacterial infection.

A study of the bone-marrow and leukocytes of the circulating blood in the present group of typhoid cases would seem to lead to somewhat the same conclusions. Basing our conception of the action of the typhoid bacillus upon the theory formulated by Welch, it seems probable that in typhoid fever the bone-marrow is affected in a

manner similar to the lymph glands, spleen, and lymphoid follicles of the intestines. It is possible that the action of the typhoid bacillus is directed primarily against the series of lymphoid or non-granular cells of the bone-marrow, and, as happens in the mesenteric lymph glands and lymphoid follicles of the intestines, these cells undergo hyperplasia. On the other hand, the increased numbers of lymphoid cells may be the result of an overproduction of these elements made necessary by a demand from other parts of the body upon the bone-marrow for these cells. In this connection Opie[28] has shown that under certain conditions one type of marrow cell, namely, the eosinophilic myelocyte, may undergo marked hyperplasia. In experimental infections of animals with trichina the local accumulation of enormous numbers of eosinophilic leukocytes forms, as Opie believes, a drain upon the bone-marrow, and to repair this loss the eosinophilic myelocytes of the bone-marrow are greatly increased.

In uncomplicated cases of typhoid fever the demand for polymorphonuclear leukocytes does not exceed the normal, and there is accordingly no reason for a hyperplasia of granular myelocytes. Under these conditions many adult polymorphonuclear leukocytes remain in the bone-marrow.

It is not inconceivable that many of the lymphoid cells found in the bone-marrow may gain access to the blood stream, and thus give rise to the increase in mononuclear elements so typical of the blood picture in typhoid fever. To sustain this view is the fact that in long-standing cases or in the latter weeks of the disease the lymphoid hyperplasia of the bone-marrow is much more pronounced than in the early stages of the attack. Moreover, it is to be noted in this connection that, according to Magrath, Brinckerhoff, and Bancroft,[29] the peculiar leukocytic reaction of variola is dependent upon the alterations in the hemopoietic organs. Characteristic of the blood picture is an increase in the mononuclear cell-type members of the leukocytic series which do not occur in the blood normally. Equally characteristic of the bone-marrow changes is a hyperplasia of the large mononuclear basophilic cells, or premyelocytes. The authors believe that the mononuclear leukocytosis is due to a disturbance in leukocytogenesis, and that owing to an inability of the bone-marrow to produce adult cells, dependent upon a failure of cell differentiation, the

mononuclear leukocytes are called from the bone-marrow into the circulating blood.

Not only does the lymphoid hyperplasia of the bone-marrow in typhoid fever seem to explain the hypoleukocytosis with mononuclear increase, but it would also seem to throw some light on the leukocytic reaction in complicating infections. It is possible after hemorrhage, when we may fairly assume that the polymorphonuclear leukocytosis is a repair process for a loss of cells from the circulation, that the granular myelocytes are capable of reacting sufficiently to overcome the damage. In secondary infections, however, it would seem that the primary typhoidal infection actually inhibits to a certain extent the formation of granular myelocytes, and hence the production of polymorphonuclear leukocytes. In not one of the fifteen cases of typhoid fever complicated by secondary infections was there a very appreciable hyperleukocytosis. It is possible that there is some functional disturbance of the large lymphocytes or premyelocytes which hampers the formation of granular myelocytes. The close relationship that is supposed to exist between these two types of cells has already been mentioned.

The reaction of the granular myelocytes seems to depend partly upon the severity or upon the type of secondary infection. In a complicating pneumonia, where, as in the present cases, there is a marked actual increase in the numbers of granular myelocytes of the bone-marrow, these cells may be produced and may form adult polymorphonuclear leukocytes in sufficient quantity to supply the demand, but not to exceed the number called for. Under such conditions an equilibrium would be established and the peripheral blood would show little or no total increase in polymorphonuclear leukocytes.

If, however, there is an excessive local call for polymorphonuclear leukocytes as well as a marked intoxication, such as might occur in perforation, this blow to the series of granular cells, combined with the action of the typhoid infection upon the non-granular mononuclear series, would lead to profound functional disturbance of the bone-marrow cells. The condition might be similar to Bunting's experiment with large doses of myelotoxin, and in fact the picture which the marrow presents in such cases suggests in a mild degree his descriptions of the marrow after the paralyzing dose of myelotoxin.

With this partial functional destruction of the leukoblastic tissue the progressively falling leukocyte count seen in many of the cases is readily understood.

SUMMARY. The bone-marrow from twenty-six cases of typhoid fever showed certain definite and constant histologic lesions. These lesions resembled very closely the changes in the mesenteric lymph nodes, lymphoid follicles of the intestine and spleen. The alterations were characterized by the presence of many lymphoid cells, large phagocytes, and foci of necrosis. There was more or less hyperplasia of the blood-forming cells. In many of the marrows from cases dying of perforation and general peritonitis there were, besides the disseminated foci of necrosis, diffuse degenerative changes in blood-forming cells, accompanied with marked edema and congestion of the tissues. Differential counts of the bone-marrow cells from ten cases showed a marked relative increase of the lymphoid cells over the granular myelocytes.

The bone-marrow from fifteen cases of acute lobar pneumonia, four cases of peritonitis, one of acute cerebrospinal meningitis, one of retroperitoneal abscess, and one of puerperal septicemia, all showed the same variety of alterations, differing in many important points from the cases of typhoid fever. There was more or less extensive hyperplasia of the blood-forming cells, with a marked relative increase of the granular myelocytes over the lymphoid cells. In the cases of peritonitis due to causes other than typhoid perforation, diffuse degenerative changes were absent. In no cases of this group were foci of necrosis found. Large phagocytic cells were exceedingly rare or entirely absent.

The bone-marrow from four cases of chronic nephritis and one of carcinoma of the gall-bladder showed no distinctive pathological alterations, and seemed to resemble very closely the marrow from two normal individuals.

It is possible that the lesions in the bone-marrow in typhoid fever are in some way nearly related to and perhaps responsible for the hypoleukocytosis characteristic of the disease. It is also very probable that the lesions in the bone-marrow in acute lobar pneumonia, peritonitis, etc., are in close association with the hyperleukocytosis so often seen in these conditions.

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December 22, 1904.

Proceedings

of the

Pathological Society of Philadelphia.

New Series, Vol. VIII. No. 3, 1905

TABLE OF CONTENTS.

Ewing, Some Aspects of the Problem of Immunity in Typhoid Fever. Annual Address.—Fife and Ravenel, Tabes Mesenterica Due to the Bovine Tubercle Bacillus.—Coplin, Modifications and Improvements in the Petri-Dish-Plate-Glass-Gelatin Method of Mounting Glass Specimens.—Anspach, Two Specimens of Pregnancy Complicated by Fibroid Tumor of the Uterus.

Some Aspects of the Problem of Immunity in Typhoid Fever.

Annual Address.

By JAMES EWING, M.D.

Typhoid fever presents with unusual distinctness some of the fundamental problems of immunity against bacterial infection. This disease, like all others, has its special features, but, being marked by a prolonged and continuous reaction of the organism against parasitic invasion, it offers unusual opportunities for the study of advanced phases of this reaction which are missing or obscure in the more acute or more chronic infections. This theoretical interest and the urgent practical importance of typhoid fever as well have influenced the choice of a subject for discussion at this time.

I propose to consider how far the known facts have succeeded in explaining immunity in typhoid fever, and to attempt to answer the concrete question, Why does one patient recover and another die in the uncomplicated course of this disease? As such an undertaking requires one to pass far beyond the range of established fact, I must ask your indulgence in dealing with the hypothetical parts of this paper.

Progress in the knowledge of immunity has chiefly followed analysis of the mode of action of bacteria in disease. When it was found that filtrates from cultures of the diphtheria bacillus are highly toxic and produce the symptoms of this disease, a curative antitoxic serum was soon perfected, which neutralizes the toxins in the circulation.

The same success was obtained in experimental tetanus and in these two diseases are the chief representatives of pathogenic bacteria that produce disease mainly through the action of soluble toxins. These toxins are called soluble because they readily split off from the bacterial cell, probably by simple hydrolysis, and they consist of proteid molecules or of poisonous radicles in proteid molecules.

But it soon appeared that very few pathogenic bacteria discharge soluble toxins into their fluid media, and that filtrates of most bacterial cultures if fresh are not very toxic, do not produce specific symptoms, and do not yield curative sera when injected into animals. Bacillus typhosus is the best known of this class of bacteria, and it may briefly be said, not to delay in the preliminary part of the discussion, that immunity against typhoid infection involves the destruction of the bacterial cell in the blood and tissues and not merely the neutralization of a soluble toxin secreted by bacteria lying chiefly in the intestinal mucosa. Recent bacterial studies of the blood have shown that in typhoid fever, pneumonia, and other diseases of this class bacteremia is usually, if not always, an early feature of the infection. In typhoid fever the bacteria in the blood are most abundant early in the disease, gradually diminishing in both fatal and favorable cases, and disappearing in favorable ones. Immunity against bacillus typhosus is not obtained by injections of filtrates, but only after the use of the bacterial cell bodies; and the antiserum does not simply neutralize a toxin, but disintegrates the invading bacillus. In the mechanism of bacteriolysis there is involved the interaction of a stable specific immune body, Ehrlich's amboceptor, and a labile non-specific agent, the complement, a ferment-like body possibly derived fom the leukocytes.

There is no doubt that these familiar and elementary principles of bacteriolysis apply to typhoid infection and that the immunizing organism dissolves the invading typhoid bacillus, but their application seems to have complicated rather than simplified the problem of immunity in the disease, or at most they have only served to disclose the complex nature of the real problem. Some of these complications may now be pointed out:

1. While most normal sera dissolve many typhoid bacilli in the test-tube, the concentrated serum of an actively immunized animal, instead

of showing an increase in this power, usually dissolves few and may fail to inhibit in any demonstrable degree the growth of typhoid bacilli in cultures. Moreover, inactivated immune serum to which normal serum is added to supply complements is not bactericidal in normal concentration. Neisser and Wechsberg offer an ingenious explanation of this phenomenon, namely, the theory of diversion of complements. Briefly this theory points out that in immune serum the molecules of an immune body greatly outnumber the molecules of complement, and in shed blood both exist to a greater or less extent in the form of complement-amboceptor combinations with free amboceptors in excess. Coming in contact with bacilli the receptors of the bacilli are occupied largely by free amboceptors, which, finding no complement not already bound to amboceptors, are unable alone to complete the destruction of the bacteria.

Injected into the peritoneal cavity of an immunized animal typhoid bacilli are nevertheless promptly dissolved, hence no diversion of complements can occur in the body.

Some serious objections to the theory of diversion of complements are encountered in the phenomena of hemolysis, and even among the reactions of organic and inorganic chemistry; and some observers, among them Bordet, refuse to accept the theory. Whatever explanation may eventually be found to apply to these facts they indicate that bacteriolysis in the immune body is not as simple and indiscriminate as the process seen in the test-tube, and that certain restrictions surround the destruction of bacteria in the body when this process serves as an effectual agent in immunity.

Since no diversion of complements occurs in the living tissues of the immune animal Metchnikoff has claimed that the complements are locked up in the leukocytes and come into play only under conditions where their action will prove most effective. He believes that in the natural process the bacteria are first loaded with immune body in the blood plasma and then englobed by phagocytes, where they are destroyed without ill effects by the intracellular complements. Wright and Douglas have recently adopted the same point of view under the newly named but identical theory of opsonines.

2. The extracellular destruction of bacteria in the body was first followed in detail by Pfeiffer in the fate of cholera bacilli injected

into the peritoneal cavity of immunized animals. There large numbers of bacilli are destroyed rather promptly by the peritoneal lymph, but not always without ill effect upon the animal. In fact, no matter how highly immune the animal is, a limit can always be found beyond which it succumbs after such intraperitoneal injection. Although the bacilli are themselves destroyed, such overdosed animals die in spite of the destruction of the living microorganisms under the condition very aptly termed "sterile death."

The existence of such an experimental condition as sterile death seems to have an important clinical significance. The bacteremia of early typhoid fever tends to diminish in the later weeks, although the patient may succumb to the uncomplicated disease. There the infection is at least limited although the patient is not saved. In pernicious malaria I have reported cases in which the blood had been freed of parasites, but the patient went on to die from the rapid cachexia of malaria. None of these cases are examples of absolutely sterile death, but they possess a suggestive resemblance to the experimental condition and indicate that the destruction of the invading parasite is not always the decisive event in the reaction of the organism against infection.

The death of the highly immunized animal after it has succeeded in killing a very large number of injected bacilli long ago suggested that the death resulted from the action of the dissolved products of the bacterial cells, *i. e.*, from the endotoxins.

The subject of the endotoxins is really one of the oldest departments of research in immunity, but it has not always figured under this name. The study of the action of the proteids of the bacterial cell was begun by Buchner and his bacterioproteins were the first isolated principles belonging to the general class of endotoxins. The separation of the specific soluble toxins of diphtheria and tetanus still left the insoluble endotoxins of the majority of pathogenic bacteria as the great problem of bacterial chemistry. From the observations on bacteriolysis, phagocytosis, and sterile death it appears that the study of the nature and action of the endotoxins contains also the real problem of immunity in most infectious diseases and especially of typhoid fever.

Of the chemical nature of the bacterial cell substance our knowl-

edge is very imperfect. Perhaps the most definite results available are those obtained by Vaughan and his pupils on the chemistry of the colon and typhoid bacilli. Splitting up the colon bacillus in bulk by dilute acids and sodium alcoholate Vaughan reaches the striking conclusion that the bacterial cell is essentially a chemical compound of definite and constant composition. From the colon bacillus he obtains a nuclein group, three amido groups, one carbohydrate, one toxic, one hemolytic, and one hemoglobin-splitting group. It has been objected that the demonstration of these groups in the products of bacteria destroyed by the violent action of acids can have no bearing on the question as to the nature of the products of this bacillus when it dissolves in the animal body. I think, however, that the objection is not thoroughly well founded. The living bacterial cell is doubtless more than a chemical compound and possesses ferment powers and possibly other properties which physical science cannot define. But when dead and disintegrating in immune serum I cannot see in the bacterial cell anything more than its chemical products. Proof is, of course, required to show that these products are the same as those split off by acids and alcohol, but there is evidence at hand that such treatment need not destroy the specific properties of bacterial proteids.

The so-called biologic properties of precipitins, and precipitable substances have been found to resist treatment by heating to 100° C., or by potassium permanganate (Obermayer and Pick) or digestion by pepsin (Jacoby). Schröder and Rettger have demonstrated amido-acids and basic compounds in the products of aseptic autolysis of bacteria and yeasts. That some at least of Vaughan's bacterial products are not seriously altered from their original condition in the living bacterial cell is shown by the fact that his colon toxin, which gives the biuret and Millon's reactions, produces immunity not only against the toxin itself but against the living bacterial cell. At any rate these studies of Vaughan furnish the most intimate knowledge we possess of the nature of the bacterial cell substance, and any discussion at the present day of the action of endotoxins must proceed from the premises he supplies. It must be admitted, however, that the further discussion of the nature and action of endotoxins involves many hypotheses.

It is probable therefore that when the typhoid bacillus is dissolved in the body somewhat similar groups to those of the colon bacillus are liberated. The toxic group may be extremely poisonous, lowering temperature and affecting chiefly the nervous system and the respiratory center. According to Vaughan the toxic group possesses haptophore and toxophore bonds and develops a new immune principle or antitoxin.

The hemolytic group must exhaust itself in dissolving red blood cells, whose products are themselves poisonous for the organism, and it may perhaps develop an antibody.

The nuclein, amido, and carbohydrate groups constitute the bulk of the bacillus, and two important characteristics of these groups seem to have demonstrated for the colon bacillus and partially also for bacillus typhosus.

First, they are intense local irritants. Vaughan found that those derived from the colon bacillus produce hemorrhagic peritonitis in guinea-pigs. Buchner's proteids, secured from comminuted bacteria by superheated steam, diluted alkali, and hydraulic pressure, were very poisonous, but not specific in their action. They were intense local irritants and powerfully chemotactic.

The uniform qualities of the products secured by Buchner and Vaughan by various methods speak in favor of the poisonous qualities of bacterial products set free in the animal body. Similar properties have been found by Kossel and others in the products of various tissue cells treated by the same methods These facts point to this class of bacterial proteids as the chief cause of the local necrotic, the chemotactic, and the inflammatory processes in different diseases.

Second, neither Vaughan's definite chemical nuclein, amido, or carbohydrate groups, nor the bacterioproteins of Buchner seem to produce immunity, but rather exert a cumulative poisonous effect on the cells, successive doses proving more and more injurious. The same rule is clearly exemplified in the course of immunization against alien tissue cells, any attempt to run up the dose of such alien proteids usually resulting disastrously, not only diminishing the lytic strength of the immune serum, but even killing the animal. For the bacterioproteins Oppenheimer concludes from his review of the literature that no evidence has been found of artificial immunity. Some of

them doubtless develop precipitins, but it is not clear how these agents assist the vital mechanism of immunity.

Pfeiffer believes that bacteria are dissolved in the body by the union of the amboceptor with a few of the many bacterial receptors; the other receptors thus set free attack the tissue cells, which throw off not antitoxins, but only lytic amboceptors. Hence the immune serum becomes increasingly bacteriolytic, while the animal becomes increasingly susceptible to the toxic action.

It is therefore very important to determine the fate of this class of endotoxins against which there is no immunity. Here there is scanty evidence to guide us, but certain probable hypotheses may be offered.

First, it seems probable that these bacterial products act as other alien proteid derivatives against which there is no immunity, and must be disposed of in the same manner. Now the nucleins, amido compounds, and carbohydrate radicles are further split up or synthesized in the body, and they are finally rendered harmless chiefly by the process of oxidation. Hence we may not be far from the truth if we suppose that these bacterial products, after seriously injuring some cells, call heavily upon the metabolic activities of the organism before they are rendered inert and excreted. Such a view has been expressed by Wolff, who regards immunity as ultimately a function of the organs, not of the serum, since these organs take care of the endotoxins.

There is some evidence in favor of this view in the histology of the viscera of animals dying from overdoses of alien proteids against which they were being immunized. I think this interpretation may safely be placed on the fatty and granular degeneration of the viscera which is constantly present in the livers of animals highly immunized against but dying from injections of alien blood cells, other tissue proteids, or bacillus typhosus. Other histologic and chemical evidence will be considered later.

In following thus far the course of the bacillus in typhoid fever, we have found that the microorganisms are first dissolved by the interaction of amboceptor and complement; that this solution, however, while limiting the growth of bacteria, at the same time liberates a series of *endotoxins*, which act injuriously on tissue cells and must be eliminated by the organs after the manner of other alien proteids and their derivatives. If dissolved in the tissue fluids or in the blood,

bacteria probably discharge a powerful toxic group (Vaughan) which contributes to the general symptoms of the disease, affecting chiefly the nervous system, while other derivatives of the bacillus are intense local irritants, dissolve red blood cells, and injure other cells with which they come in contact. If englobed by phagocytes the endotoxins are probably limited in action to the englobing cells, but their products must eventually be disposed of after the manner of other alien proteids. There is some evidence that this disposal is accomplished largely by the liver and chiefly by the process of oxidation.

At several stages of the process the organism reacts with the formation of antagonistic bodies or properties, (1) destroying many bacilli by the interaction of newly formed amboceptors, produced by injured cells and complement supplied principally by leukocytes; (2) neutralizing a specific endotoxin by antiendotoxin (Vaughan), and (3) possibly controlling the hemolytic action by an antihemolysin. Yet the bulk of the dissolved bacillus is liberated in the form of poisonous proteid derivatives against which there is no development of immunity, but which have a cumulative injurious action on the tissue cells. It will be seen that a curative bactericidal serum could stop this process only by preventing the primary invasion of the microorganism; since after the infection is established and large numbers of bacilli are present in the tissues and blood, rapid bacteriolysis becomes a menace to the organism by liberating endotoxins. Theoretically there would seem to be no hope for the discovery of a curative serum for typhoid fever after the infection has become established, while the spontaneous cure of the malady must be accomplished through a very delicate adjustment of slowly progressing destruction of bacteria, and equally important and difficult disposal of endotoxins.

But the chemical aspects of the subject probably by no means fully cover the properties of invading microorganisms. Living bacteria possess certain ferment activities such as inhere in all living protoplasm. At least six ferment actions have been demonstrated in the cultures of bacillus pyocyaneus. From the studies of Emmerich and Low, Hahn, Levy and Phersdorff, and many others, the presence of ferments in living bacteria has been demonstrated as constant properties in bacterial cells as of metazoan tissue cells. To some

extent these properties are transferred to the culture media, and they must be reckoned with in considering the action of invading microorganisms.

Some of the actions of bacterial products now commonly attributed to ferments may be shared by the inert derivatives of bacterial proteids. Jordan has recently shown the relation of alkalinity and hemolytic activity of some bacterial filtrates. Others probably belong exclusively to living bacteria, and even when shared by both living bacilli and their cast-off products, Abbott and Gildersleeve have shown for the hemolytic action of some species that the living bacillus dissolves red cells far more actively than do the filtrates or dead bacteria.

The scope of this paper does not permit the detailed consideration of the part played by this class of bacterial ferments in disease, but some general facts may be stated of them:

1. There are general ferment properties of bacteria which are not to be identified with the specific toxins of these bacteria.

2. Such ferments probably act locally on tissue cells, the proteolytic ferment, for example, bringing into solution dead tissue cells, blood cells, and possibly blood proteids. Among the products of bacterial ferments albumose must be given an important position as a source of toxic symptoms (Blumenthal).

3. The formation of distinct antibodies for these ferments is not yet satisfactorily demonstrated, although some ferments seem to produce more or less general antiferments (Landsteiner).

4. It seems probable that the bacterial ferments are prominently concerned in the autolytic disintegration of the bacterial cell and the liberation of their poisonous proteid derivatives.

Thus far attention has been devoted to the action and fate of the invading bacillus and its products, and nothing has been said of the significance of the disorganizing tissue cells and their products. Yet every dissolved red cell or leukocyte or disintegrating or necrosing tissue cell liberates poisons, and in a prolonged disease like typhoid fever especially the destruction of tissues must play a very important part in the morbid process. Aside from the highly poisonous and specific toxic group the bulk of the bacillus, according to Vaugan, is composed of non-specific proteid derivatives which in chemical com-

position and physiologic action do not differ greatly from derivatives of tissue cells. Certainly they are not more locally irritant or powerfully chemotactic than are the homologous nucleoproteid and organ extracts of the higher animals.

High leukocytoses are recorded by Goldscheider and Jacob from injections of thymus extracts. Commercial nucleoproteid of vegetable and animal origin I have found to produce widespread visceral necroses, local and general hemorrhagic exudates, and extreme leukocytolysis in rabbits. Beebe, in the Loomis laboratory, has lately killed dogs by small intraperitoneal injections of nucleohiston prepared from dogs' kidneys. According to Vaughan every cell in the animal body contains complex molecules similar to those of bacteria, and his pupils, Munson and Spencer, split off a toxin from liver cells by dilute acids.

Now, it is a very important characteristic of these non-immunizing derivatives of bacterial and tissue cells that they are not only poisonous in themselves, but possess a cumulative action and excite a self-perpetuating morbid process in the organism. Hemolytic serum which has dissolved red cells in the test-tube becomes more hemolytic (Polk) possibly from the liberation of lecithin. Clinical types of cumulative hemolysis seem to exist in the rapid impoverishment of the blood in malaria and blackwater fever and in streptococcus infections. The cumulative action of alien amido-acids and other derivatives of tissue cells may perhaps be found in the visceral lesions of immunized animals dying after overdoses of tissue cells or killed bacterial cultures, and I see no other explanation for the fulminant forms of acute yellow atrophy. The same interpretation, I believe, must be placed upon those cases of typhoid fever which die late in the disease from severe toxemia and with sudden failure of urea excretion as described by Curschman, or with hypothermia as described by Roger, or with acute yellow atrophy, to which reference will be made later. Ehrlich's theory of the *horror autotoxicus* is based upon the cumulative toxic action of dissolved tissue cells.

Considerations of this character suggest that the various clinical types and features of typhoid fever may depend not so much upon the invading microorganism as upon the effects of the poisons derived from degenerating tissue cells, and that the spontaneous cure of the

disease depends upon factors not at all or very distantly related to the destruction of bacteria and neutralization of their products. The invading bacteria doubtless initiate and perpetuate the morbid process, but even in the outbreak of the disease every one admits the importance of what we call predisposing factors, which are little else than local disturbances of metabolism or general disorders of the system, attended, as Sweet has shown in one particular, with a loss of blood complement.

I do not hope to establish this thesis, which is by no means new, in an unassailable position, since any such attempt would require a discussion of the entire subject of metabolism in febrile infectious diseases, but in these days of strenuous bacteriologic investigation I find it interesting and profitable to review some of the facts which point to the importance of morbid processes in the host as compared with those in the parasitic invader.

First, I find strong support of this theory in recent studies, which have shown that typhoid fever may be referable to infection by one of several readily distinguishable species of bacteria. As Juergens has pointed out, all known clinical types of typhoid fever have been found to be associated with infection by the bacillus of Eberth, or by paratyphoid strains or by paracolon strains. While the specific proteids and bactericidal antibodies of these species are so different that the antiserum against one may have little or sometimes no agglutinating or bactericidal effect on the others, yet the clinical manifestations and pathologic lesions of these infections are practically identical. Hence Juergens insists that we are not justified in employing the term "paratyphoid fever" when a so-called paratyphoid organism is isolated from the blood, since the Eberth or paracolon bacillus may produce the same disease. "All attempts to explain the different types of typhoid fever by differences in the type of infection have collapsed. The origin of the different types of typhoid fever seems much more dependent upon the individuality of the affected organism." If one considers as the individuality of the patient the particular course taken by his disturbed metabolism, the conclusions of Juergens express exactly the present point of view.

Again, the numbers of the infecting bacilli do not appear to be the sole determining factor in the development of a severe form of typhoid

fever. In Koch's report of the investigation of the epidemic at Trier fifty-two children were found to show typhoid bacilli in the stools, but only three had typhoid fever. The infection in these and in fatal cases came from the same source. Koch points out the necessity of caring not only for the sick, but also for the healthy, although infested, individuals in the control of typhoid epidemics. In those subjects remaining healthy the bacillus had multiplied in the intestinal tract, but had not produced the disease. Among walking cases whose stools contained typhoid bacilli, Koch collected a series of mild typhoidal disorders which would not otherwise have come under the physician's charge. This same lack of relation between intestinal infection and development of typhoid fever was observed in another epidemic in which the Schottmüller bacillus was the infecting agent (Juergens).

It may be claimed that all these considerations apply only to the bacillus in the intestinal tract, but that as soon as it invades the tissues it invariably produces the same results. But this claim is not in accordance with the facts, since all three groups of typhoidal organisms have been isolated from the blood in cases showing marked differences in type and severity.

The long persistence of the bacillus in the tissues after recovery from typhoid fever is a remarkable fact of significance in this connection. In the urine it commonly persists for weeks and sometimes for months, being discharged from foci in the kidney or multiplying innocuously in the bladder. Young found Eberth's bacillus in the urine five and seven years after an attack of typhoid fever. Houston found bacillus typhosus in a case of cystitis of three years' duration, the patient never having had a definite attack of typhoid fever. Buschke isolated the typhoid bacillus from a bone abscess seven and a half years after typhoid fever, and von Dungern obtained it after fourteen and a half years in an abscess from the gall-bladder. In considering these cases, one must remember the difficulty of positively identifying the typhoid bacillus and the possible occurrence of unrecognized ambulatory attacks of typhoid fever, yet similar observations have so frequently been recorded as to show that the spontaneous cure of typhoid fever is not attended by the destruction of all the microorganisms in the tissues or body cavities which

continue to harbor the bacteria without suffering any general or often any local disturbance. They are in accord also with the fact demonstrated by Stern, Korte and Steinberg, Hahn, and others, that there is no uniform difference in the serum of typhoid convalescents and of normal subjects in capacity to kill typhoid bacilli in the test-tube. Even in animals, according to Stern, the convalescent serum is not always more effective than normal serum, as determined by Pfeiffer's test, and Stern concludes that bactericidal action is not the agent which confers immunity, nor is it antitoxic, but something which acts on the whole organism.

It is an interesting fact also that relapses may occur when the bactericidal power of the blood is highly developed. Korte and Steinberg report illustrations of this fact, and in one instance a relapse occurred in a patient whose serum diluted 1 : 4,000,000 killed typhoid bacilli in Stern's test. These results have more bearing on the possible curative value of a bactericidal serum than upon the nature of the process excited by the typhoid bacillus when once it gains a foothold in the blood and tissues.

As a possible explanation of the development of relapses when the blood is highly bactericidal it may be supposed that all the more susceptible bacteria are destroyed with the decline in the fever, but that some have increased in resistance and at a favorable crisis succeed in multiplying sufficiently to establish a second general infection. Or it may be supposed that the blood suddenly loses its bactericidal power or its complement content, thus permitting the recrudescence. Neither of these theories seems to admit of proof by present data, and the occurrence of one or more relapses in typhoid fever must stand as a very obscure feature of this infection, and one which indicates that recovery from this disease depends on something more than bactericidal activity of the blood and neutralization of specific endotoxins.

A peculiar lack of relationship between the severity of the disease and the occurrence of bacilli in the blood appears in some bacteriologic studies. Hewlett observed a very toxic case of typhoid fever in which his usually successful cultures by Castellani's method failed to show any bacilli in the blood on the sixteenth and twentieth days, but were later successful in a relapse. After the third week his cul-

tures were nearly all sterile, even in very severe cases. In one case cultures were negative during a sharp initial attack, but positive during a very mild relapse.

Cole also reports a fatal case in which three cultures were negative. These results are not numerous and are difficult of interpretation, but they seem to indicate that the severity of typhoid fever is dependent on some other factor than the presence of demonstrable number of bacilli in the blood.

It is a well-known fact that tyhoid epidemics differ in severity, and the virulence of the infecting strain is doubtless a very important factor in this respect. Yet the severity of the disease is not always parallel with the virulence of the bacterium. In the Trier epidemic some virulent races were obtained from mild cases and slightly virulent races from severe cases. As a rule, the virulence as ordinarily measured increases during growth in the host, cultures from the spleen being usually more virulent than those from the stools of the same patient.

In considering virulence it is necessary to distinguish between invasive capacity and toxicity.

According to Theobald Smith's conception the biologic purpose of parasitism is not to poison the host, but to multiply the bacterial species. He believes that during parasitic existence bacteria tend to lose toxic qualities and develop powers of resistance. This point of view is borne out in some respects in the case of the typhoid bacillus. Passage through animals diminishes agglutinability and susceptibility to bactericidal serum, but increases the invasive capacity of the strain. Vaughan's pupil, Gelston, finds that the poisonous activity of the typhoid toxin split off by hydrolysis is in inverse ratio to the virulence of the strain. If he identifies virulence with invasive capacity, the observation further supports Smith's view that parasitism tends to diminish poisonous properties, and it also helps to explain the apparent absence of definite relation between the virulence of the infecting bacterium and the severity of the disease.

If the above conclusions are reliable, then the great severity of some epidemics in army camps must be due to greater invasive properties of the bacteria acquired by frequent passage through several hosts, and not to greater activity of their specific poisons. Reaching the tissues

in larger numbers more endotoxins must be cared for by the organism, and this factor must influence the severity of the disease. That it is not the sole determining factor, however, appears from the continuously negative results of blood cultures in some severe cases followed by successful cultures in mild relapses.

The study of metabolism in typhoid fever furnishes the deepest insight into the nature of the morbid process, and indicates that the specific bacterial poison can directly account for only a small part of the disturbance of the organism.

There are two phases of this extensive subject to which attention may be drawn, viz., the alkalescence of the blood and the nitrogenous metabolism.

Regarding the nitrogenous metabolism in typhoid fever there are two main facts bearing on our problem: (1) the prodigious increase in the urea nitrogen of the urine and (2) the increase of ammonia and amido-acid nitrogen.

According to von Jaksch's analyses the daily excretion of urea nitrogen in several cases amounted to 12 to 19 grams per diem, a figure approached only in diabetes, while the amido-acid nitrogen reached as high as 0.5 gm., an amount equal to that in diabetes, leukemia and icterus gravis, which are among the most prominent autointoxications.

The significance of this large quantity of urea nitrogen is only appreciated when one considers the limited diet of these patients as compared with that of diabetics. It is evident from the recent literature on amido-acids in the urine that there is no thoroughly reliable method for the quantitative estimation of these principles in urine, but the above studies are sufficiently clear in their results to warrant the conclusion that in severe typhoid fever there is a distinctly pathologic quantity of amido-acids in the blood, and that in this respect the blood of the critical typhoid patient resembles that of the early stages of acute yellow atrophy. In a series of cases of yellow atrophy collected by Richter the urea nitrogen ran between 75 and 90 per cent. of the total nitrogen, falling to 50 to 60 per cent. before death. In Richter's case the urea nitrogen continued at about 79 to 85 per cent. until the day before death, when it fell to 61 per cent. The ammonia nitrogen formed about 7 to 16 per cent. of the total nitrogen.

The following distribution of the nitrogen of the urine was determined for me by Dr. C. G. L. Wolf, in a case of typhoid fever toward the end of a rather severe relapse, temperature 102° to 103°: Total nitrogen, 11.65 grams; urea nitrogen, 9.33 grams, or 80 per cent.; free ammonia nitrogen, 0.865 gram, or 7.4 per cent.; amido-acid nitrogen, 1.26 grams, or 10.9 per cent. (Pfaundler's method); uric acid nitrogen, 0.14 gram, or 1.3 per cent.

In this case the nitrogen partitions are nearly identical with those of the early days of Richter's case of acute yellow atrophy.

The condition of the liver in fatal typhoid fever fully supports this conclusion. An advanced grade of acute granular and fatty degeneration with myriads of focal necroses are constant histologic lesions of the liver. This subject has been ably presented before this Society by Mallory in 1898. The same lesions occur numerously in the spleen and kidney, and Fraenkel and Longcope have recently described them in detail in the bone-marrow. In a considerable number of cases this process produces a liver greatly reduced in consistence and somewhat reduced in size.

Roger has drawn special attention to an hepatic type of typhoid fever in which there are severe intoxication, falling temperature, and advanced degenerative changes in the liver.

If the process in the typhoid liver is really identical in kind with that of acute yellow atrophy, there ought to be occasional instances of a pronounced grade of acute yellow atrophy in typhoid fever. The literature furnishes many such cases. They are rather more frequently reported in the older writings, when less was known about typhoid fever, but quite as much if not more about acute yellow atrophy.

Frerichs describes two cases in his classical work on *Diseases of the Liver* (1858). Oppolzer also reported a case in 1858. Diett (quoted by Griesinger) and Liebermeister noted the occurrence of acute yellow atrophy late in typhoid fever. Hoffmann described the condition in his work on *Pathological Anatomy of Typhoid Fever*. According to Lancereaux, Andral and Louis described cases of icterus gravis in typhoid fever, with leucin and tyrosin in the urine. Sabourin described a case in which the microscopic lesion seems to have been intermediate between focal necrosis and diffuse destruction of hepatic

parenchyma, while the gross appearance was that of well-advanced acute yellow atrophy. In Dörfler's case the hepatic lesion was complicated by cholelithiasis and old obstruction of the cystic duct, to which, however, he attributed no relation to the hepatic lesion. That the older clinicians regarded the hepatic lesions of typhoid fever as of constant occurrence and of fundamental importance appears from the following quotation from Frerichs, written in 1858: "In typhus the secreting function of the liver is impaired at an early period, the evacuations become pale, and a grayish, greenish fluid, which, as a general rule, contains leucin, is found in the gall-bladder. The formation of sugar, as well as the elaboration of bile, is diminished, and usually is soon completely arrested. At the same time substances find their way into the secretion of the gland, which, under normal conditions or in other diseases, are either absent or exist in much more sparing quantity. We find leucin and usually also tyrosin in considerable quantity; a substance resembling xanthin, and hypoxanthin, and also, according to Scherer, occasionally cystin. The secretion is frequently neutral and contains ammonia. We have examined the liver in a large number of diseases, and have arrived at the general result that in typhus fever, etc., the substances mentioned exist in unusual quantity, whereas in pneumonia, etc., they are absent or present in very sparing quantity. . . . There can be no doubt that these derangements react upon the composition of the blood. The presence in the urine of leucin, etc., shows that these derangements are not of a limited character, but that their products pass into the blood and the excretions."

In many recent studies of focal necroses of the liver the histology and pathogenesis of these lesions have been very fully discussed, but their clinical importance has barely been mentioned. During the past year I have been engaged in comparing the clinical symptoms, the histology and chemistry of the liver, and the chemistry of the urine, in various diseases showing such diffuse and focal lesions of the liver. The external circumstances surrounding this work render progress very slow, but I can say that considerable evidence has been collected to show that the above lesions of the liver are always associated with a pronounced grade of intoxication, which, in its severe forms, resembles that of idiopathic acute yellow atrophy. Since the exact

source and nature of the toxic agents in acute yellow atrophy are not fully understood, it is, of course, possible that this disease in its fulminant forms involves some factors which may be missing in other diseases presenting very similar hepatic lesions and urinary changes.

Connected with observations on the histologic lesions of the liver and their relation to metabolism are the results of numerous studies on the alkalescence of the blood, some of which may be very briefly reviewed. Fodor, Behring, and Calabrese found that the blood of animals, increased in alkalescence by various methods, proved uniformly more bactericidal, while Roux and Nocard observed diminished bactericidal power of the blood with diminished alkalescence. Zagari demonstrated that alcohol, hunger, and physical exertion diminished both alkalescence and bactericidal power. Fodor observed that the blood of rabbits receiving injections of typhoid cultures lost greatly in alkalescence if the animals died, but very little if they survived and gained in weight. In Rigler's comprehensive studies, six cases of typhoid fever which recovered showed alkalescence only slightly greater than a fatal case of phosphorus poisoning. In animals receiving injections of bacillus typhosus he found a more rapid and extensive loss of alkalescence than from some other bacteria—*e. g.*, bacillus diphtheriæ, staphylococcus, bacillus of Friedländer. In view of the possible relation between blood alkalescence and disturbance of the urea-forming function of the liver in typhoid fever, it is of interest to note that he found ammonium carbamate to distinctly diminish blood alkalescence. In general, he concluded that blood alkalescence is not a specific property directed agaist bacteria and is not identical with the properties which rid the blood of bacteria and their toxins, but is the expression of a general reaction of the organism, which is essential to recovery from infectious processes.

It is an interesting fact, also, that many of the conditions showing diminished alkalescence of the blood are also marked by loss of complement and follow excessive demands on the oxidative capacity of the organism.

Finally, must be mentioned some miscellaneous features of the nitrogenous metabolism of typhoid fever. The high proportion of ammonia nitrogen in the urine was first demonstrated by Duchek and verified by Köppe and Hallervorden. According to Van Noorden,

it may run as high as 8 to 12 per cent. of the total nitrogen as against the normal 5 to 7 per cent. Its excess indicates, in general, deficient oxidation and acidemia. Beta-oxybutyric acid has been demonstrated in typhoid urine by Van Noorden, who regards its presence as a sign of an acid intoxication in the disease. The diazo reaction of the urine appears to be more constant in typhoid fever than in any other disease. Although the substances on which this reaction depends have not been determined, it is generally regarded as a sign of seriously disordered nitrogenous metabolism, which belongs in general to those clinical conditions known as the typhoid state. According to Clemens, who has carefully considered the chemical relations of the subject, it probably depends on some incompletely oxidized products of nitrogenous metabolism belonging among the aromatic compounds. The uniform occurrence of these unoxidized bodies in the urine of typhoid fever and in many other severe toxic states which have the clinical aspect known as the "typhoid condition" indicates that the disturbance of metabolism in all these states has some features in common which are not dependent on any specific microorganism.

The recent observations on Ehrlich's new benzaldehyde reaction indicate that the urine in infectious gastroenteritis contains other unknown and somewhat specific derivatives of abnormal proteid metabolism.

Finally, it may be mentioned that Symmers has found the organic or unoxidized phosphorus of the urine much increased in typhoid fever and some other diseases.

Since the foregoing discussion has led into rather widely differing fields of research, before attempting any general conclusions, it becomes necessary to recapitulate.

Following the guidance of recent studies in immunity, the action and fate of the invading microorganism in typhoid fever have been partially traced. It has been found that one of several distinct but related strains of bacteria may invade the organism and induce the same disease in properly disposed individuals; that this bacterium multiplies in certain tissues and in the blood until its growth is inhibited and the bacterial cells are dissolved. The destruction of the bacterium, however, is not without danger for the organism, since

the dissolved bacterial cells liberate endotoxins, some of which may be neutralized by antibodies; but other more numerous derivatives, exerting an injurious effect on tissue cells, cannot be so neutralized, and must be disposed of by other metabolic processes in the body, in which oxidation probably takes a prominent part. The local and general effects of all these endotoxins initiate a series of changes in various tissue cells, with destruction of large numbers of these cells and the liberation from them of other poisonous principles, and these combine with the bacterial endotoxins in producing the symptoms of the disease.

It has been shown that neither the virulence nor the variety of the infecting bacilli wholly account for the clinical differences in the course of the disease; that this course has no uniform relation to the bactericidal power of the blood; that relapses occur where the blood is strongly bactericidal, and recovery may follow when this property is relatively deficient; that all the bacteria are not killed till long after defervescence, and some frequently remain long in the body cavities or tissues without producing much local or general reaction.

So much in review for the parasite and its relation to the disease, but pathologic anatomy and the chemistry of metabolism indicate that the reaction in the host is very much more extensive and complex than can be accounted for through the direct action of the bacteria and their products. There is an extensive loss of body weight, with enormous excretion of urea nitrogen and excessive demands on the oxidative capacity of the organism. There are intense degenerative changes in the viscera, leading to necroses in the liver, kidney, and lymphoid organs, sometimes leading to degenerative atrophy of the liver, and apparently always attended by the presence in the blood of toxic products of nitrogenous metabolism and diminished alkalescence, and with leucin, tyrosin, aromatic acids, etc., in the urine.

Some clinical and experimental data go to show that these degenerative changes, while initiated by the non-specific bacterial proteids, possess certain self-perpetuating tendencies, since many of the derivatives of both bacterial and tissue cells exert a cumulative action and fail to produce antibodies and immunity.

The general conclusions which the preceding discussion seems to warrant may now be stated.

Typhoid fever is a combination of a specific bacterial intoxication and a somewhat peculiar autointoxication, the former element being more prominent early, the other later in the disease, but both developing simultaneously. The latter conception dominated the views of clinicians in Griesinger's time, when little was known of the infecting agent, while the former aspect of the disease has held almost exclusive attention since the discovery of the typhoid bacillus and with the recent remarkable progress in the study of bactericidal immunity. As too much importance was once undoubtedly given to the host, so it would seem that the present tendency is to magnify unduly the part played by the parasite. Both factors must be studied together if a correct conception of the disease is to be reached.

A practical bearing of the discussion concerns the serum therapy of the disease. It is becoming more and more evident that the value of a bactericidal serum in well-established cases of typhoid fever must be very doubtful. Bactericidal sera are curative in inoculated rabbits, but these animals do not have typhoid fever. Such sera may prove effective in the early stages of some infections in man if the bactericidal power is deficient, but it is difficult to see how it can be other than a dangerous agent in later stages of the disease, when the bactericidal power is commonly high and the organism is suffering from the bacterial endotoxins and from the poisonous products of its own cells.

Chantemesse reports a mortality of 6 per cent. in 500 cases of typhoid fever treated by an elaborately prepared bactericidal serum, but these results are little if any better than those obtained in some hospitals by the cold-bath treatment and irrigation. It is not by any means certain that the results obtained in Paris could be duplicated in Chickamauga or Philadelphia. So far as I can learn, all attempts to support the bactericidal serum by introducing foreign complements have failed in man, though more successful in animals.

The prevention of the disease by active immunization, as instituted by Wright, has much better theoretical basis, and its practical results, which are very difficult to estimate, seem to have been fairly successful.

It is not my desire, however, to engage in an *a priori* argument against such a serious and concrete ambition as the serum therapy of

typhoid fever. The foregoing discussion seems far more important as offering encouragement to the more thorough study of typhoid fever by the clinician, the pathologist, and the physiologic chemist.

In the severe stages of the disease there is much to be hoped from such studies as those of Cushing and Clarke, who have endeavored, by more elaborate internal hydrotherapy, to assist the organism in its burden of eliminating alien and endogenous poisons.

If the foregoing argument has been at all sound, then we must look to the general pathologist for the solution of a large part of the problem of immunity in typhoid fever, through a more exact study of the pathogenesis of the disease. It has recently been hinted from high authorities that the day of the old-fashioned general pathologist is passed. It does not appear that the leading Continental pathologists have been much disturbed by this suggestion, and I do not myself partake of this view. I believe there remain fundamental observations still to be made at the autopsy table, and equally important interpretations still to be drawn from the histologic study of diseased viscera. According to E. Albrecht, present histologic methods tell us what we do not want to know about the cell. This remark appears especially true when we consider our utter inability to predicate from the morphology of a cell its functional capacity. Doubtless the aid of the physiologic chemist is essential in this field, but the pathologist and chemist working together are needed to elucidate many of the problems concerned in the development of typhoid fever and many other diseases. The chief factors determining the onset, the course, and the relapses of typhoid fever are not all to be found in the characters of the receptors of the typhoid bacillus, but one would not gather this impression from the bulk of recent literature on typhoid fever. Important facts regarding immunity in typhoid fever have been contributed by experiments decided in the test-tube, and later by the study of fresh blood under a cover-glass, but the full problem can only be reached in the pathologic anatomy of the viscera and in the chemistry of the viscera, blood, and excretions of the typhoid patient.

Finally, the question remains, To what extent are the general autotoxic features of typhoid fever shared by other diseases? On this point I believe it may be said that after the specific features of various infec-

tious diseases have been referred to the specific action of bacterial toxins and to particular locations of the inflammatory processes, there remains a considerable element which is practically identical in them all, and that this element will permanently resist all attempts of serum therapy. In these days when the multiplicity of the facts and conditions concerned in the development and course of infectious diseases staggers the mind, any unity which can be demonstrated in them all may perhaps be welcomed.

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April 27, 1905.

Tabes Mesenterica Due to the Bovine Tubercle Bacillus.

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AND

MAZYCK P. RAVENEL, M.D.

It is our intention at this time simply to report a case of tuberculosis of the mesenteric and retroperitoneal glands, with associated fibroid peritonitis, from which bovine tubercle bacilli have been isolated.

Our patient was a male, born in February, 1901; died in January, 1903. He was the sixth child of healthy parents. All his brothers and sisters were apparently healthy before the death of our patient, but since then the oldest sister, his nurse, has developed cervical adenitis. The family of ten lived in five small, dark, poorly ventilated rooms in a crowded neighborhood. The maternal grandfather, a maternal granduncle, and a maternal grandaunt died of phthisis; otherwise the family history is negative.

For the first seven weeks of the child's life the nourishment consisted of breast milk, but from the seventh week until the end cows' milk was the chief food, although some table food was given after the ninth month. The milk was obtained from various sources, but most frequently from corner grocery stores. It usually contained a dirty sediment, and was rarely Pasteurized.

The mother states that the child was always puny, and that his development was markedly less rapid than that of his brothers and sisters. In his fourth, sixth, and eleventh months he had enterocolitis. Between these attacks the bowels were alternately constipated and loose, but the periods of diarrhœa were much the longer. The stools always contained mucus, usually curds, and during the last year of life undigested solid food.

When the child was about thirteen months old the mother noticed a marked swelling of his abdomen. The enlargement became more and more marked, and a prominent practitioner made the diagnosis of "enlargement of the colon," and told the mother that she must knead the abdomen vigorously if she would save her child. This kneading treatment was carried out under the direction of the doctor

for about two months, although the procedure seemed to cause intense pain. It is possible that this had some relation to the retroperitoneal peritonitis. The conditions not improving, the mother consulted numerous physicians and received various diagnoses, including cyst of the left kidney, sarcoma of the kidney, acute distention of the colon, and tuberculous peritonitis. The diagnosis of "sarcoma" was made under ether anesthesia by a skilful pediatrist, examination per rectum convincing him that there was a postperitoneal mass. The diagnosis of "cyst" was made by others because of apparently distinct fluctuation in the kidney region. It seems possible, in the light of the postmortem findings, that this fluctuation may have been due to caseation in the enlarged postperitoneal glands.

The child came under our observation during the last few weeks of his life and had then slight irregular temperature and alternating diarrhœa and constipation. Physical examination revealed marked emaciation and anemia, enlarged hard cervical and inguinal glands; a practically negative chest; a very tender, tremendously distended, drum-like abdomen, with no special point of prominence; an easily palpable tumor in the left lumbar region, which was apparently movable, but did not seem to move with change of position of the child, and no fluctuation could be detected in it; a second small movable tumor, the width of one's finger and about one and one-half inches long in the right umbilical region; no ascites; no abdominal friction sounds. The percussion note over the left hypochondriac and left lumbar regions (area of palpable tumor) was dull; inflation of the colon seemed to lessen the area of dulness, but did not obliterate it. The urine was negative. Only one examination for the tubercle bacillus was made, results being negative. Bronchopneumonia developed just before death.

Dr. Alfred Hand helped to make the autopsy. There was considerable difficulty in opening the abdomen because of adhesions of the abdominal contents to the parietes. The omentum was bound down to the intestine, was contracted, but it did not form the distinct cord-like tumor to which Gairdner has called special attention. The stomach, liver, and spleen were bound down, but not very firmly. The liver was only slightly adherent to the dia-

phragm; the intestines throughout their length were so firmly matted together and so firmly attached to the omentum that it seemed impossible to extricate them. It was even with the greatest difficulty that the kidneys were reached through the abdominal incision because of the dense adhesions. When the intestines were freed from the abdominal walls, the tumor which we had palpated in the left lumbar region was found to be in the median line. This tumor was a mass of mesenteric and postperitoneal glands in which loops of small intestines were firmly embedded. The adhesions around these mesenteric glands were by far more dense and apparently older than any others. Other mesenteric glands besides those involved in the tumor were enlarged and some were caseous. The mesentery throughout was thickened; there were several small nodules on the great omentum, and a few tubercles on the liver, spleen, and diaphragm, but these were chiefly superficial on the visceral peritoneum. No tuberculous lesions were found on the mucous surfaces of the intestines, but a thorough examination was impossible because of inability to lay open the intestines the entire length. The colon was distended. The pericardium and pleuræ seemed free. No enlargement of the anterior mediastinal or of the bronchial glands. The lungs were those of bronchopneumonia. The focus of infection seemed unquestionably in the mesenteric and postperitoneal glands.

A portion of one of the mesenteric glands was excised, ground in a mortar with sterile salt solution, and injected into the peritoneal cavity of three guinea-pigs. The first animals all showed a mixed infection, due mainly to the colon bacillus, and re-inoculation was necessary. Great difficulty was experienced in obtaining a pure tuberculosis. Cultures were finally obtained from the spleen and omentum of a guinea-pig, on dog serum with 5 per cent. of glycerin. The bacilli were found to stain evenly and deeply and to show no beading, though somewhat more slender than is usual with the bovine tubercle bacillus. Growth was slow and not abundant, and it was not until the third generation that enough could be obtained for the inoculation of animals.

On November 26, 1903, a calf weighing 211 pounds was inoculated after having been tested with tuberculin, and found free of

tuberculosis. After inoculation the temperature rose gradually, reaching 105° on December 7th, after which it fell and remained comparatively low for four or five days. The calf showed marked signs of illness, the temperature rising again to 105.8° on December 15th, and to 107° on December 20th. From this time it varied from 105° to 107°, the animal growing rapidly more ill. Death took place on December 31, 1903, thirty-five days after inoculation.

Postmortem. The animal was much emaciated. In the peritoneal cavity a small amount of bloody fluid was found. The liver was pale and fatty, showing a few nodules. On microscopic examination numerous localized areas of necrosis and round-cell infiltration were found. The spleen appeared to be normal. The kidneys were normal to the naked eye, but on microscopic examination numerous tubercles and some giant cells were discovered.

The lungs were free from adhesions. On section they were found to be bright red throughout, and there were innumerable nodules evenly distributed, and 1 mm. to 4 mm. in diameter. The largest of these were caseous in the centre. On microscopic examination tubercles of varying ages were found in large numbers, with many giant cells. Sections stained with carbol fuchsin showed innumerable tubercle bacilli.

On December 21, 1903, rabbits and guinea-pigs were also inoculated. The rabbits lived longer than is usual when inoculated with the bovine tubercle bacillus, but died of a generalized tuberculosis, involving the lungs, liver, spleen, and kidneys, a result not obtained with the human bacillus in our experience, when the dose is very minute and placed under the skin, as in this case.

The guinea-pigs all died with generalized tuberculosis. These animals are so susceptible to both the human and the bovine tubercle bacillus that they are useless for differentiation between the two types.

Conclusion. The tubercle bacillus obtained from the mesenteric gland in this case, though slightly atypical in morphology, and perhaps attenuated to a very slight degree in virulence, must be classed as a bovine organism. As the child was fed during practically the whole of its life on cows' milk, the conclusion seems justified that the infection was from this source.

Discussion.

Dr. Coplin asked whether the lesions were those of human or bovine tuberculosis.

Dr. Ravenel said that Hueppe specially insisted that Koch never produced bovine lesions even with bovine bacillus, if the histologic characteristics are considered distinctive. Dr. Ravenel's experience in the laboratory of the State Live Stock Sanitary Board has been similar, bovine bacilli never having produced bovine tuberculosis—that is, perlsucht, or grape disease. The only instances in which bovine lesions were produced were those in which the inoculation was with a human bacillus. As to the distinctions between the lesions histologically, Baumgarten and others have shown that the lesions are practically identical up to a certain point, and then the human lesions tend to caseate, while the bovine tend to calcify rapidly. *December* 22, 1904.

Modifications and Improvements in the Petri-Dish-Plate-Glass-Gelatin Method of Mounting Glass Specimens.

By W. M. L. COPLIN, M.D.

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C. J. Patten,[1] Professor of Anatomy, University College, Sheffield, suggests a method of mounting anatomic specimens for museum purposes, using a plaster-of-Paris slab, upon which permanent orientation is accomplished. Immediately after reading Prof. Patten's paper it occurred to me that the principle involved could be applied to the Petri-dish-plate-glass-gelatin method.[2] Dr. Funke was kind enough to make some preliminary experiments, which resulted in our adopting the following procedures:

The glass plate upon which the mount is to be made is thoroughly cleaned and a temporary receptacle made upon it by four strips of wood, 0.5 cm. in thickness, laid upon the surface in such a way as

[1] British Medical Journal, November 19, 1904, p. 1378.

[2] Journal of the American Medical Association, August 13, 1904.

to form a rectangular well, 0.5 cm. in depth, the smallest transverse measurement of which exceeds by 0.5 cm. the diameter of the Petri dish to be used in the mount. The strips of wood, or, better, glass, are weighed or clamped in place. For the preparation of the plaster matrix the formula recommended by Prof. Patten has been adopted, except that we use what is called "dental" plaster of Paris; 27 ounces (approximately 830 gm.) are mixed with 22 ounces (approximately 680 c.c.) of water, this affording a mixture that sets smoothly and is of satisfactory consistency. Into the temporary vessel constructed on the surface of the plate glass the prepared plaster is poured, carefully avoiding air-bubbles. While still soft the preparation to be mounted is removed from the final Kaiserling preservative, quickly blotted on a towel or filter paper, and gently bedded in the soft plaster. In order to rarify the contained air, the Petri dish is inverted, slightly warmed, and then pushed down over the specimen in the plaster until the margin of the dish rests firmly upon the plate glass. So soon as setting is complete the excess of plaster on the outside of the dish is removed, this part of the plate and dish cleaned, and the sealing completed with balsam. To prevent the growth of moulds on or around the specimen, it might be well to press into the plaster of Paris a crystal of thymol or possibly a small lump of camphor.

By the method just suggested the specimen is mounted in an air space unsurrounded by gelatin and containing no fluid. We have no preparations mounted sufficiently long to determine how well these will keep, but gelatin preparations similarly mounted have been preserved for more than a year. The method used by Littlejohn[1] is practically dry. The jars are closed with glaziers' putty. He strongly commends the method for toxicologic specimens, especially when the lesions result from carbolic acid or the mineral corrosive acids. The color preservation he regards as satisfactory, even after five or six years. At the last meeting of the American Medical Association, Dr. Wynn showed specimens preserved for months in Petri dishes which were not even sealed. If the foregoing methods are satisfactory, it is reasonable to assume that material will keep in the plaster-embedded condition.

[1] Journal of Pathology and Bacteriology, 1903, vol. viii. p. 360.

As just described, but one surface of the specimen can be inspected, but it seems possible that the method could be so applied as to expose both sides of the specimen. In order to accomplish this, one surface of the mount should be fastened to the plate glass by means of formalized gelatin (gelatin containing 0.75 per cent. of formalin), and the walls of the temporary well for receiving the fluid plaster made of such a height that when filled to the necessary depth its contents will not overflow the enclosed specimen; the Petri dish is applied as already directed. So mounted both sides of the preparation could be inspected.

It also seems possible that these mounts could be made without the use of a Petri dish, but along this line of the inquiry we are unprepared to make any positive statements. A specimen of which it is desired that only one side should be exhibited could be cemented to the glass plate by means of formalized gelatin, and, as soon as the gelatin has set, liquid plaster poured over it should afford sufficient protection; the plaster might be rendered impervious by subsequent treatment with warm wax or oil, such as are used for painting on plaster.

The Petri-dish-gelatin mounts may be made more valuable if each preparation be accompanied by a section so placed that it can be subjected to microscopic examination. Every teacher knows how slides are prone to stray just when most wanted, and in order to avoid this difficulty the histologic preparation is made a part of the macroscopic mount. This is easily accomplished by fixing paraffin sections to a cover-glass by the albumin or other satisfactory method, removing the paraffin and subsequently treating the section exactly as though it were on a slide, except that the final mount is made near one corner of the glass plate instead of on a slide. In order to examine this mount a block just the height of the microscope stage is placed to one side and slightly in front, so as to share with the microscope stage the support of the plate glass.

Discussion.

Dr. Ravenel said that some specimens mounted in plaster appeared to have sweated. This, and the fact that the specimens appeared very wax-like, seemed to him to be objections to the methods.

Dr. Coplin said that the sweating results chiefly from changes of temperature, and is slight when these changes are slight. It occurs more markedly in gelatin specimens than in plaster-of-Paris specimens. *January* 26, 1905.

Two Specimens of Pregnancy Complicated by Fibroid Tumor of the Uterus.

By BROOKE M. ANSPACH, M.D.

In both cases the diagnosis was made before operation. In both radical operation was necessary because of the anatomic relations of the tumors. The first case was in a young woman who had been recently married and who, when about three months pregnant, developed symptoms indicating severe intrapelvic pressure. A large subperitoneal and numerous interstitial fibroids were found upon examination to be blocking the pelvis. No symptoms of fibroids had been present before.

It is not uncommon to find that fibroids or the symptoms from them first appear during pregnancy, the increased blood supply during this period favoring their rapid growth. They at times become smaller, subsequent to pregnancy, undergoing involution with the uterus itself, but it is questionable whether they recede to their previous size in any considerable number of cases.

In the second case intraligamentary myomata were present and would have formed an insuperable obstruction to labor. Operation in this case was carried out at the end of the third month.

Complication of pregnancy by fibroid growth is particularly interesting pathologically, because fibroids are most common in women who have never borne children, and sterility has been cited as a large factor in the production of fibroids. The question is yet unsettled whether a fibroid growth prevents impregnation or whether the continuous menstrual activity of the nulliparous woman leads to the fibroid growths. It is most likely that fibroids are of congenital origin and that, because of the distortion of the uterine cavity that they occasion, there is difficulty in the ingress of the spermatozoa and also in the embedding and nourishment of the ovum. *January* 26, 1905.

Proceedings

of the

Pathological Society of Philadelphia.

New Series, Vol. VIII. No. 4, 1905

TABLE OF CONTENTS.

Rosenberger, A Study of Homogenized Cultures of Tubercle Bacilli.—Bergey, Influence of Pasteurization on the Chemical and Physical Qualities of Milk.—Coplin, Celluloid Strips and Sheets for the Orientation of Gross Preparations, Especially Spinal Cords, during Fixation and Handling, and also to Facilitate the Identification of Parts Removed for Microscopic Examination.—Funke, Syphilis of the Liver (Sclerogummatous Type).

A Study of Homogenized Cultures of Tubercle Bacilli.

By RANDLE C. ROSENBERGER, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

The growth of human, bovine, fish, or avian tubercle bacilli in bouillon has a tendency to form a scum or pellicle, and in the absence of this, under ordinary conditions, no growth is obtained. This pellicle may be started by floating a small mass of the transplanted culture upon pieces of cork (Coplin), or by using sterile oil for the float, and the floating can be accomplished without either cork or oil if great care is exercised not to wet the whole mass.

To obtain what is called a homogenized culture quite different technique is employed. The first to call attention to this special cultivation of the tubercle bacillus was Ferran,[1] who recommended inoculating into a series of bouillons successively poorer and poorer sugar and glycerin. Arloing[2] recommends for the preparation of cultures for the agglutination test, potato, which is placed in a tube containing a quantity of a 6 per cent solution of glycerin, just

[1] Société de biologie, 1897; Archives générales de médecine, January, 1903.

[2] Comtes-rend. de l'Acad. des Sci., 1898, vol. xxii. p. 319.

sufficient to touch the lower end of the potato. After inoculation the tubes are kept in the incubator at 38° to 39° C. On every second day the tubes are tipped so that the glycerin solution is made to flow over the culture on the surface of the medium. Under these conditions growth occurs rapidly, the resulting masses of bacilli differing from those in ordinary cultures in that they are soft in consistency, and easily broken up by a glass rod or by rubbing in a mortar. From these cultures subcultures are made in veal broth, and submitted to daily shakings to keep the organisms separated from one another; though even in these preparations it is impossible to prevent some clump formation. The majority of the organisms are isolated, however, and the fluid is turbid, and shows but little sediment. According to Courmont and Descos, the more numerous the transplantations the better the resulting homogeneity. When pseudotubercle bacilli are experimented with, a scum is likely to form in a few hours, so that repeated shakings are absolutely necessary; with the bacillus of human tuberculosis, since the film does not form until several days of repose, there is less trouble in obtaining homogeneous cultures.

Hawthorn[1] recommends growing the tubercle bacillus in a medium consisting of peptone (Defresni) 20 grams, sea-salt 7 grams, water 1 litre; neutral to litmus, but faintly acid to phenolphthalein.

Auclair[2] gives the following technique for obtaining a homogeneous growth, and, at the same time, a saprophytic form of the tubercle bacillus. The organism is sown on a beef bouillon containing potato, salt, sugar, and glycerin. At the end of twenty days it will be found that the previously clear medium has become slightly cloudy without the formation of a pellicle, but later with a tendency toward the development of a deposit.

The writer's experiments in obtaining homogeneous cultures of tubercle bacilli were made by using glycerin agar and glycerin potato growths, and inoculating into a 5 per cent. glycerin bouillon. The agar preparations were made originally from a homogenized bouillon culture. The method of inoculating the bouillon consisted in taking

[1] Comptes-rend. Soc. de biol., 1903, vol. v. p. 398.
[2] Arch. de méd. exper. et anat. path., July, 1903, p. 469.

upon a platinum-wire loop a small portion of the growth from potato and rubbing it thoroughly upon the side of the tube or flask. The bouillon was brought in contact with the growth by rotating the receptacle, thus washing off and at the same time disseminating the organisms throughout the medium. The culture was placed in the incubator at 37° C., and several times a day, at least twice, the flask was shaken to prevent the bacteria precipitating or forming a pellicle. Growth of the human tubercle bacillus was noticed as early as the third or fourth day, when turbidity of the medium was apparent. The cloudiness persisted and increased and resembled vigorous cultures of the bacillus typhosus. If the flask was not shaken a very granular and amorphous sediment formed. In all these cultures, in addition to the sediment, pellicle formation took place, and when this was shaken down, another formed in a couple of days. In one preparation a third pellicle developed, though it was more scanty and delicate than the two previous ones. When glycerin agar was inoculated from a bouillon culture, growth was usually observed within five to seven days; the fully formed preparation was moist or creamy in appearance and consistency, and could be easily removed and readily spread upon other culture media. A perfectly homogenized preparation will remain turbid indefinitely, but eventually a sediment forms or a pellicle appears. The writer was also successful in obtaining a perfectly homogenized preparation of the human tubercle bacillus in plain bouillon at the temperature of the body and at ordinary room temperature. In the incubator at body temperature growth was abundant and appeared as early as the fifth day, while at ordinary room temperature only slight turbidity was noticeable at the end of two weeks. The method of inoculation was the same as mentioned for the ordinary homogenized preparations. The appearance of cultures in plain bouillon was exactly like those in glycerin bouillon. In homogeneous cultures of the human tubercle bacillus the morphology and microchemical reactions are but slightly different from growths upon blood serum or upon glycerin agar.

Auclair claims that the homogeneous tubercle bacillus is a strict aërobe; the elements longer and larger than the ordinary bacterium and the organism actively motile. Hawthorn states that the motility

of tubercle bacilli upon his special medium is most striking, and notes the presence of free spore-like bodies. Arloing maintains that the homogenized tubercle bacilli are motile; from Arloing's description of these motile forms of the organism Koch doubted the identity with his own bacillus. Loeb[1] denies motility, though the usual Brownian movement is present. The writer was unable to demonstrate motility in any of the cultures examined, even in cultures only four or five days old. Brownian movement was evident in nearly all preparations. Marmorek asserts that homogeneous cultures when young lose their virulence and in part their resistance to acids. In the writer's experiments young homogenized bacilli resisted 25 per cent. solution of sulphuric acid just as markedly as preparations from an agar culture. In morphology the human tubercle bacillus was very pleomorphous, exhibiting short and long forms; some of the former were so small that they were almost coccoid, while the latter were filamentous in nature. Beaded forms were common; club-shaped bacilli and branched organisms were occasionally encountered. In cultures three months old the individual elements were very long, 10 to 12 microns being an average size. Some were thin, others thick; some stained darkly, the remainder stained very faintly. Quite a few contained small, deeply stained granules which slightly exceeded the diameter of the organism itself. As many as eight of these granules were observed in a single element. This filamentous character was quite constant, the threads resembling closely those seen in streptothrices. Large, thick, irregularly staining or beaded forms were common in old cultures. Although the greater number of the organisms were isolated and ungrouped, there was a decided tendency to collect in small masses of from six to twelve or fifteen elements. Five c.c. of the homogenized bouillon culture inoculated into the peritoneal cavity of a guinea-pig produced caseous nodules ranging in size from 5 mm. to 2 cm. Spreads made from these lesions contained numerous beaded, long, acid-fast bacilli.

Homogenized cultures were also made of the bacillus tuberculosis piscium, bacillus tuberculosis avium, as well as of Moeller's grass bacillus.

[1] Journal of the American Medical Association, May 23, 1903.

B. tuberculosis piscium. The individual elements were pleomorphous. Small coccoid forms were abundant in young preparations, while suggestively filamentous forms were present in older cultures. The average length of the organisms was about 2 microns. Beading was also noticed and in this form the bacterium is stained less darkly than the other solidly staining elements. No clubbed bacilli were present, and, although pairs were frequently observed, isolated bacteria predominated; the tendency to form in groups was not especially noticeable. They were non-motile, but an active Brownian movement was apparent. Resistance to 25 per cent. solution of sulphuric acid was still retained in old cultures, though to a certain extent lost in very young growths.

B. tuberculosis avium. Like the previous organisms, this bacterium was also pleomorphous. Very small, almost coccoid forms were present; others were from 5 to 6 microns in length. The long form showed a decided tendency to club formation, while a smaller, thin variety appeared as if fractured near the centre, causing it to resemble a diplobacillus. Beaded bacilli, but no filaments, were present in young cultures, though the latter form was abundant in preparations six months old. The tendency to form in groups was decided, although individual bacilli were present in every field. There was not the slightest Brownian movement or motility of any kind noticeable in young or old cultures. Resistance to 25 per cent. solution of sulphuric acid was well preserved.

Moeller's grass bacillus. This organism was taken as the type of the pseudotubercle bacilli. The individual elements in cultures two weeks old were short, stout, and oval; very few, if any, long forms, and no beaded or clubbed forms were seen. Some bacilli were decolorized by 25 per cent. solution of sulphuric acid, while the greater number still resisted the reagent. An agar culture made from the homogenized preparation was of the color and consistency of cream. Spreads made from this growth contained many long and beaded forms, which were quite resistant to 25 per cent. solution of sulphuric acid.

Discussion.

Dr. Coplin: Referring to Dr. Rosenberger's observation that his cultures were not motile, and to the differences of opinion concerning this point, said that the variations might be the result of physical or chemical conditions of the media rather than differences in the bacteria themselves. He suggested the possibility of modifying the virulence of tubercle bacilli by prolonged cultures under abnormal circumstances, such as those in homogenized cultures. This might ultimately have therapeutic value.

Dr. Ravenel said that he had never seen motility in individual bacilli in homogenized cultures, but agglutination is easily seen, nevertheless. One culture Dr. Ravenel has had under observation for four years still preserves its original morphologic characters, including the acid-fast property, though the cultures have been homogenized throughout this period. Arloing and Courmont and most other Europeans use 2 per cent. of peptone in growing the homogeneous tubercle bacilli for agglutination work. Dr. Ravenel got his best results with only 1 per cent. of peptone, and Dr. Baldwin, of Saranac, had had the same experience.

February 23, 1905.

Influence of Pasteurization on the Chemical and Physical Qualities of Milk.

By D. H. BERGEY, M.D.

(From the Laboratory of Hygiene, University of Pennsylvania.)

The limited extent to which I have studied the influence of Pasteurization on the keeping qualities of milk precludes the possibility of formulating any definite conclusions. At present I shall only give the results of the studies that I have made so far and indicate in a general way the influences observed. The complexity of the problem makes it impossible to do more than this.

My observations were made altogether on samples of milk procured in open market and Pasteurized in sterilized glass-stoppered

bottles in the laboratory. If these observations differ in any particular from those obtained with commercial Pasteurized milk it is probable that such differences must be due to the conditions under which the samples were obtained.

In order to comprehend the influence of Pasteurization it will be necessary to indicate the results of detailed studies as to the nature of the bacteria found in the raw and Pasteurized portions of a given sample of milk. The raw milk, if derived from healthy cows in a clean dairy, will contain relatively large numbers of the group of lactic acid bacteria. Along with the lactic acid bacteria we also find several varieties of spore-forming bacteria which for convenience of classification may be designated the subtilis group. The lactic acid group brings about the souring of the milk and induces the formation of the curd. In a clean milk the subtilis group usually plays very little part in the alterations that take place in the milk during the first forty-eight hours. There are probably two principal reasons why the subtilis group of bacteria usually has so little influence: first, the relatively small numbers of these bacteria originally in the milk, and, second, the apparent inhibiting powers of the lactic acid group, or their products, upon the growth and activity of the subtilis group. I have, on several occasions, seen evidences of this inhibiting influence of the lactic acid group on the subtilis group in milk Pasteurized at low temperatures. In such samples the subtilis group was present at first in relatively small numbers and later became very much diminished in numbers.

In a clean, normal market milk the age of the milk is generally indicated by the activity of the lactic acid bacteria, inasmuch as the degree of acidity follows more or less closely the age curve. In such a milk curdling takes place in a period of time which varies with the temperature and coincides with a certain degree of acidity and the presence of a fairly definite number of bacteria. The rapidity with which these alterations in the milk are produced is influenced by the temperature at which the milk is kept. At the temperature of the ice chest curdling rarely takes place by the third day, and it is frequently postponed until the fifth or sixth day, or longer. By the time curdling has taken place in such a milk the number of bacteria has increased from a few thousand up to millions, while the

acidity has increased to 10 or 12.[1] At the room temperature and at the body temperature the alterations are practically the same, but they occur earlier, though in regard to the time of curdling wide variations are noted in different samples of milk, even in samples derived from the same dairy on different days.

In market milk that is not very clean the subtilis group of bacteria will frequently be present in sufficient numbers to materially modify the rate and character of the alterations that take place in the milk. It is, therefore, impossible to state offhand the keeping qualities of a particular sample of milk because there is no means of foretelling the relative numbers of the two principal groups of bacteria contained in it.

Pasteurization of the milk serves to remove the lactic acid bacteria while it leaves the number of bacteria of the subtilis group practically unchanged, because these are not destroyed by the degree of heat employed in Pasteurization. For this reason the alterations noted in a sample of Pasteurized milk differ considerably from those taking place in the raw milk. The subtilis group of bacteria produces a lower degree of acidity in the milk than does the lactic acid group, but at the same time it may bring about more rapid curdling. The subtilis group possesses the property of bringing about proteolytic changes and by this means it may induce more or less rapid digestion of the albuminous constituents of the milk, thus rendering it entirely unfit for consumption. For these reasons the degree of acidity of a Pasteurized milk is no criterion as to its richness in bacteria. For instance, while a raw milk at the temperature of the ice box at the end of five or six days shows an acidity ranging from 10 to 12, the same milk when Pasteurized and kept under similar conditions for the same length of time may show an acidity ranging from 2 to 3.5. As an illustration of the results obtained with the raw and Pasteurized portions of a sample of milk kept in the ice chest I will give the following:

[1] In this connection it is necessary to state that the acidity of the milk was determined by the direct titration of 10 c.c. of the milk without dilution. The indicator employed was phenolphthalein. Comparative tests have shown that this method gives somewhat higher results than when the milk is previously heated and diluted with water.

	Bacteria at once.	*Bacteria at 72 hours.*	*Reaction.*	*Coagulation.*
Raw,	1260	17,250,000	10.4	+
Pasteurized,	12	148,500,000	3.4	+

Two other portions of the same sample of milk kept at the room temperature yielded the following results:

	Bacteria at once.	*Bacteria at 72 hours.*	*Reaction.*	*Coagulation.*
Raw,	1260	5,475,000	11.2	+
Pasteurized,	12	66,700,000	5.6	+

These results indicate that Pasteurization removes the most important indicator furnished by nature to announce the approach of the possible danger limit in the particular sample of milk. In Pasteurized milk the acidity may be but little above the normal and yet the bacteriologic analysis will show very large numbers of bacteria. Such a condition appears to be due to the fact that the Pasteurization has removed the lactic acid group of bacteria and has given full sway to the activities of an entirely different group of bacteria, most of which are not very active acid formers.

Dairymen and creamery men make use of the sense of taste and smell in judging of the character of a sample of milk. It requires a carefully cultivated sense of taste to judge milk accurately by this means, and I have not attempted to make any observations along this line. The odor of milk also requires a cultivated sense, though, in a general way, I believe it would be possible to obtain confirmatory evidence of the condition of milk in this way. The fact that I kept all my samples of milk in sterile glass-stoppered bottles seemed to me to assist in rendering this test of some value. The results obtained, however, indicate that this method did not afford reliable data. This may be due, in part at least, to lack of a properly cultivated sense. Of course, when the odor had become pronounced the bacterial content and physical and chemical condition of the milk were also indicative of a bad milk. But during the first forty-eight hours there was frequently no very definite alteration in the odor of a sample, though its bacterial content and degree of acidity were both quite high.

The odor of different samples of milk kept under identical conditions is subject to such wide variation that this factor is only of

secondary value in determining the character of any sample. For instance, one of the samples of Pasteurized milk placed in the ice chest had a sweet odor on the fourth day, though it contained 27,600,000 bacteria. Of course, when the odor of a sample of milk indicates that it is bad, all the other tests coincide.

Observations were also made on the time of coagulation in order to ascertain the character of the milk when this change takes place. Beginning coagulation in a sample of raw milk indicates the presence of from 10,000,000 to 100,000,000 bacteria, and an acidity of about 10. Curdling begins at from twenty to twenty-four hours at the body temperature, while at lower temperatures it may be postponed for several days. In Pasteurized milk, kept at the same temperatures, curdling usually does not take place as early and the degree of acidity is uniformly lower—usually 6 to 7.5. Pasteurized milk frequently begins to curdle when the bacteria present range from 3,000,000 to 10,000,000, though I have encountered samples of Pasteurized milk with more than 20,000,000 bacteria without any evidence of coagulation. (Studies in detail shown in table.)

The results of the studies I have made indicate that no single test serves to portray accurately the true condition of a sample of Pasteurized milk. The test which seems to be of most value is the bacteriologic examination. Unfortunately, this test, like all bacteriologic tests, requires elaborate paraphernalia and consumes considerable time.

The fact that Pasteurization leaves an unopposed field to the activities of the subtilis group of bacteria, and hence that such a milk may become unfit for use even earlier than a raw milk, because of the very rapid miltiplication of this group of bacteria, should receive special emphasis. Pasteurized milk, because of the nature of the bacteria remaining in it, should receive even greater care in the house than raw milk; it should be kept at a low temperature during and after distribution, and should be used as soon as possible.

We have no knowledge of any direct injurious influence of the bacteria of the subtilis group on the health of human beings, yet it is probable that the metabolic products of these bacteria, when present in milk in considerable amounts, will exert injurious effects, especially in young infants.

February 23, 1905.

Comparison of Results Obtained with Raw and Pasteurized Milk.

No.	RAW MILK. Bacteria at once.	24 hours. Bacteria.	Odor.	Coag.	Reaction.	48 hours. Bacteria.	Odor.	Coag.	Reaction.	PASTEURIZED MILK. Bacteria at once.	24 hours. Bacteria.	Odor.	Coag.	Reaction.	48 hours. Bacteria.	Odor.	Coag.	Reaction.
ROOM TEMPERATURE.																		
1	120,000	10,375,000	Stale.	—	4.35	10,900,000	Cheesy		9.65	10	192,250	Sweet	—	2.10	4,830,000	Cheesy		7.45
2	142,750	10,175,000	"	—	7.55	27,150,000	"	+	12.25[1]	275	750	"	—	2.35	11,615,000	Stale	—	7.30
3	29,808,000	113,600,000	"	—	5.20	151,300,000	Rancid		10.10	32	?	"	—	2.20	1,650,000	Rancid	—	6.40
4	400,000	48,300,000	"	—	2.90	69,000,000	"		10.30	12	782,000	Stale	—	2.05	220,080,000	"		8.85
TEMPERATURE OF ICE CHEST.																		
1	.....	5,850,000	Stale	—	3.65	7,475,000	Stale	—	6.60	...	31,000	Sweet	—	2.00	1,495,000	Stale	—	2.20
2	.....	1,495,000	"	—	2.85	23,950,000	"	—	8.90	...	?	"	—	2.15	40,000	Sweet	—	2.30
3	.....	9,500,000	"	—	3.20	156,400,000	"	—	9.30	...	500	"	—	2.00	600,000,000	Stale	—	2.80
4	.....	10,800,000	"	—	2.45	37,950,000	Rancid	—	8.50	...	?	"	—	2.05	351,000	Rancid	—	3.55
BODY TEMPERATURE.																		
1	.....	48,700,000	Rancid		9.20	24,150,000	Rancid	+	14.20	...	9,225,000	Rancid	+	6.90	3,750,000	Rancid	+	9.40
2	.....	72,850,000	Stale		10.00	69,575,000	"		25.15	...	30,875,000	Stale	—	7.50	49,850,000	"	+	10.65
3	.....	187,950,000	"		9.30	586,500,000	"	+	11.30	...	?	"	+	6.40	475,000	"	+	9.90
4	.....	118,450,000	Rancid		9.15	63,525,000	"		12.30	...	4,354,000	"	+	6.70	35,000,000	"	+	11.45

[1] Some of the bacterial counts as given for 48 hours were obtained at 72 hours. Likewise some of the tests of acidity were made at 72 hours, instead of at 48 hours.

Celluloid Strips and Sheets for the Orientation of Gross Preparations, Especially Spinal Cords, during Fixation and Handling, and also to Facilitate the Identification of Parts Removed for Microscopic Examination.

By W. M. L. COPLIN, M.D.

(From the Laboratories of the Jefferson Medical College Hospital.)

These strips consist of clear or gray celluloid, and measure 41 cm. in length, 4 cm. in breadth, and 0.3 cm. in thickness. The sides and ends are notched, the notches being 2 cm. apart; one face of the strip is roughened that it may be written upon with a lead-pencil. The removed cord attached to its membrane is secured in position on this strip by means of threads passing through the membrane and around the strip upon either side and the ends resting in the notches. If the cord be mounted a little to one side a free margin remains upon which figures may be placed identifying the parts to be studied, or parts removed for examination. The method recommended is that the upper end of the strip should be marked by a number, which in the note-book corresponds with the number of the cord or case; Roman numerals had best be used for this marking. If the numbers down the side of the strip are in Arabic, there should be no difficulty in keeping segments or blocks so that they readily may be identified and accurately placed.

The unroughened and unnotched strips cost $1.50 per dozen. A janitor can roughen them in a few minutes with sand-paper; the notches are made with an ordinary triangular file.

Strips of hard rubber, preferably red, may be used in the same way, but are more fragile. The roughened red rubber strips can be written upon with an ordinary pencil; such writing is read with difficulty on black rubber, but legends (ordinary labels) may readily be attached with celloidin or celluloid cement.

The plan just described may be applied to large masses or slabs of organs, as, for example, brain. In most instances thread cannot be used for attaching the specimen; when one surface is flat celloidin or gelatin (formalized) may be used.

The technique for attaching a slab of any tissue, for example, brain, is as follows:

The roughened surface of the celluloid sheet is cleaned and dried. The slab of tissue is removed from the fixative or other solution, rinsed in water and then in alcohol and quickly blotted dry. A sufficient quantity of thin celloidin is poured on the roughened and dry surface of the celluloid plate, and the slab of tissue, with the appropriate side upward, is pushed firmly into the still liquid celloidin and held in place for two to three minutes, by which time it is sufficiently adherent to be immersed in the preservative, which may be any of the fluids commonly used. The celluloid plate may be written upon with the ordinary graphite pencil and the positions of any blocks of tissue removed can be indicated by letters or numbers. The strips of celluloid may be used repeatedly, as any marks upon them can be erased. I have tried a number of inks for writing upon celluloid, but as yet have found none satisfactory.

Discussion.

Dr. McCarthy thought the method valuable for teaching purposes, but less so in actual neuropathologic studies; for in the latter the real interest lies in the secondary degenerations, and in investigating these in the spinal cord one must determine the definite source of interesting sections, not by the vertical elevations from which they were taken, but by the situation above or below certain individual nerve roots. With the brain the use of slabs of tissue would make it difficult to follow the degenerations. With the brain Dr. McCarthy determines the source of blocks of tissue by making them of different shapes, in accordance with the portion of a convolution from which they are taken. This makes it necessary only to know the convolution from which they came.

Dr. Coplin considered Dr. McCarthy's objections reasonable, but in many specimens (for example, syringomyelia) ordinary methods are useless or nearly so, because of the distortion of the cord.

January 26, 1905.

Syphilis of the Liver (Sclerogummatous Type).

By JOHN FUNKE, M.D.

(From the Laboratories of the Jefferson Medical College, and from the Philadelphia General Hospital.)

Although Fischer maintained that syphilis produced five different lesions in the liver, yet he recognized that the forms are not easily separated from one another. The classification given by Virchow is the one usually accepted. He maintained that syphilis may affect the liver as a diffuse process or as a gumma, or these two may be combined, giving us a sclerogummatous form. Frerich recognized a waxy or amyloid type, but this has been excluded by Virchow. It is the sclerogummatous form that will be dealt with here. This paper is based upon a liver obtained at autopsy at the Philadelphia Hospital. The pathologic diagnosis was as follows: Chronic ulcerative tuberculosis of the lungs, hyperplastic pleurisy, fibroid myocarditis, hyperplastic splenic capsulitis; chronic interstitial nephritis, miliary tuberculosis of the liver.

Since no lesion in the other organs bears upon the matter under consideration, the postmortem findings in the liver and gall-bladder only will be given. The liver lacked 1 cm. of reaching the costal margin in the midclavicular line; it was slate colored, but had a distinct greenish tinge; the organ was firm and scattered over its external surface were many round or oval grayish areas, varying from 2 to 4 mm. in diameter. They were apparently beneath the capsule, which seemed involved. This was clearly shown to be the case by sectioning; when incised they were found to extend into the parenchyma of the organ to a distance of about 2 to 4 mm. Over the external surface, 5 cm. to the right of the suspensory ligament, were two depressed grayish-white lines running nearly parallel with that structure; they were both 4 mm. in width; one measured 2.5 cm. in length and the other 1 cm. The organ was found to resist the knife, and the cut surface was studded with nodules similar to those described as being present under the capsule. They resembled miliary tubercles in every respect, although it was quite impossible to remove what appeared to be caseous centres. The peripheries of many of the

lobules were easily outlined and were slightly depressed; the depressed parts were grayish-white in color and resembled fibrous tissue. The greenish tinge was more pronounced on the cut surface than upon the external portion of the organ, giving the parenchyma a granular appearance. Near the transverse fissure of the organ was a fibrous mass, 1 cm. to 2 cm. in size, which incorporated the bile passages, but did not impinge upon the vessels. A probe introduced at the ampulla of Vater extended as far as the juncture of the hepatic and cystic ducts, where it met with an obstruction, and, upon dissection of the common duct, the lumen was found occluded by the fibrous mass already mentioned. Upon further dissection the cystic duct also was occluded; the right hepatic could not be traced, but the left branch passed near the margin of the fibrous mass. The fibrous nodule extended into the liver for a distance of 1 cm. At no point in the growth could either duct or liver substance be identified; apparently it was fibrous throughout and distinctly circumscribed. The greatest diameter of the gall-bladder was 7.5 cm.; the organ reached 10 cm. below the margin of the liver, was soft and elastic, and apparently filled with fluid, but the distention was so marked that fluctuation could not be elicited. At the junction of the gall-bladder with the liver was a mass of cicatricial tissue which formed firm adhesions between the two organs. The scar was pinkish-red in color and very tough. The gall-bladder was found to contain 225 c.c. of a slightly cloudy, grayish-tinged fluid. Its mucous membrane was covered by a grayish-white, semisolid mucigenous substance; when the latter was removed the exposed mucosa was pale and smooth. The walls of the gall-bladder were extremely thin, scarcely 2 mm. in thickness. The peritoneal cavity contained 150 c.c. of a straw-colored fluid.

Cumston maintains that the deep indentations along the anterior border of the organ and the white lines running over the external surface of the liver are characteristic of syphilis, and he refers to Virchow the statement that they occur most frequently in the neighborhood of the suspensory ligament and that the convex surface is a frequent site. After fat metamorphosis, he says, the gummata are absorbed and replaced by fibrous tissue. In discussing the morbid anatomy of syphilitic cirrhosis of the liver, Hale-White says the puckering and the scarring are unlike that of atrophic cirrhosis. In

syphilitic disease the scars are big and broad, sometimes one-third of an inch in width; they cut the liver into large areas, as big as the back of one's hand; never do we see the little hobnail projections which are so characteristic of ordinary cirrhosis of the liver. Lazarus-Barlow reports a liver with syphilitic stricture of the bile-ducts. The organ was dark green from retained bile, and it was almost entirely composed of an enormously hypertrophied left lobe. The right lobe was small and its surface was covered with numerous old scars and deep indentations, the seat of old gummata. One mass of fibrous tissue, he said, involved the bile-ducts; the left hepatic duct was separated from the common by a thin fibrous septum. MacKenzie reported a liver which was uniformly enlarged, and had two scars on its surface. The gall-bladder was distended with a colorless fluid, and its duct was so embedded in fibrous tissue that the lumen was occluded. He believes that the scars on the surface of the liver are retrocedent gummata and calls attention to the fact that the cut surface of the organ strongly suggests the presence of malignant disease.

In the case herein reported the microscope did not corroborate the diagnosis of tuberculosis of the liver based on examination of the gross specimen. Although the indentations and the scarring already referred to by Cumston, Hale-White, Lazarus-Barlow, and MacKenzie were not evident macroscopically, they are very clear microscopically. The dipping is marked even at points where the underlying parenchyma is not involved. The perihepatitis which, according to some authors, is a frequent accompaniment of this form of lesion and to which Stockton ascribes the pain and the friction, is not marked in this case. The capsule is thickened at points, and this hyperplasia is greatest where the fibrous tissue extends into the parenchyma of the organ. The tissue responsible for the thickening is composed of coarse, wavy fibrils, which react to Mallory's reticulum stain, as do the fibrils making up the normal capsule. Between the fibrils are many lymphoid cells which are evenly dispersed and show little tendency to grouping.

As pointed out by Cumston, the fibrous tissue is abundant throughout the sections, and as noted by Hawkins, Quincke, Cumston, and MacKenzie, it not only surrounds the lobules, but penetrates these structures as coarse and fine strands. The picture presented is such

as might have been produced had the newly-formed tissue originated at the periphery of the lobule and by continued proliferation gradually extended between the liver cells, and as it did so impinged upon them, whereby they were destroyed; close examination of the sections stained with Mallory's reticulum stain seems to justify the view that the newly formed intralobular tissue is an increase of the already existing reticulum. At many points it is possible to see how along one side of the bloodvessels nests of liver cells have been isolated by the increased reticulum, and how difficult it is to outline or even trace the reticulum between the liver cells on the opposite side of the same vessel. In an area where the fibrous tissue is abundant it is evident that toward the periphery of the fibrous mass delicate strands of newly formed tissue surround retrogressing liver cells. The picture presented in many respects is similar to that described as present around some of the bloodvessels. Near the centre of the tissue such nesting of the liver cells cannot be found. Here the newly formed tissue is closely matted and between the wavy fibrils are many lymphoid cells. In many places the distribution of the fibrous tissue is similar to that seen in atrophic cirrhosis of the liver, that is, from a central focus, very often a bloodvessel, it tends, in the majority of instances, to surround each lobule separately, but occasionally embraces several. A frequent picture is the occurrence of circular masses of newly-formed tissues, the centres of which are occupied by bloodvessels whose walls are thickened, but not in proportion to the thickening seen around the bile-ducts; the elastica does not figure in the increase.

Distributed throughout these nodular masses are many bile-ducts the walls of which are also thickened by concentric layers of newly formed tissue. The columnar epithelial cells, fairly well preserved, occur as usual in a single layer. The circular or perhaps nodular masses of fibrous tissue are responsible for the gross picture which was interpreted as miliary tuberculosis. Although nearly all authors point out that there is an increase in the intralobular connective tissue, none refer to that seen around the central vein, which, while not marked, is readily demonstrable in the sections.

Adami maintains that in the acquired form of syphilis there is a generalized toxic distribution in the organ, with a resulting catarrhal

hepatitis, which may or may not lead to a general fibroid condition. Flexner is of the opinion that interstitial hepatitis is due to a diffuse poison, perhaps a toxin elaborated by the syphilitic virus or organism. The lesions of syphilis, he says, are comparable to those produced by the bacillus tuberculosis which sometimes gives rise to a diffuse fibroid growth; at other times produces tubercles. A careful histologic study of the sections in this case lends support to these opinions. The distribution of the fibrosis may be explained in the following way: The toxic substance is brought to the liver by the portal vein and hepatic artery; probably most of it reaches the organ by the former route. We know that the interlobular veins break up into numerous capillaries at the periphery of the lobule, thus increasing the vascular area, and this is instrumental in slowing the blood current so that the liver cells at the periphery of the lobule are most severely affected by the syphilitic poison; these cells degenerate or undergo necrosis, the reticulum is irritated, either by the poison itself or by the products of the degenerated cells, and as a reactionary process the reticulum, together with the interlobular tissue, is increased.

Scattered throughout the sections, although not so numerous, are circular or oval cellular areas which at times involve an entire lobule. They are composed, for the most part, of large cells with palely staining nuclei resembling the hyaline leukocytes; although there are some polymorphonuclear leukocytes present, they are not increased over the number found in other portions of the liver. In the centres of the areas are many granular and fragmented cells and considerable granular detritus; liver cells cannot be identified; here the accumulation of hyaline cells is not so great as farther toward the periphery. Most of the accumulated cells are surrounded by newly formed fibrous tissue, except in a number of instances, where the encircling sclerosis is incomplete and the gap is filled with long spindle cells closely resembling those commonly seen in the formative tissue. These isolated patches were at first taken for abscesses, but upon finding polymorphonuclear cells as abundant in the liver tissue elsewhere, their presence was looked upon as being incidental. Bacteria could not be demonstrated. Closer study suggested miliary gumma.

Marchand, when speaking of the cellular infiltration of syphilitic

livers in infants, tells us that although the greater number of cells are mononuclear, many are polymorphonuclear. According to this author, even if the polymorphonuclear cells are not found in the other parts of the organ, their presence need not rule out miliary gumma. Hawkins maintains that the miliary gummata are rare, while Quincke says they are less frequent than the diffuse form, but when found they are scattered throughout the liver in abundance and resemble tubercles or neoplasms. He notes that deformity of the organ is less likely to occur in the miliary than in the gummatous form. Adami found giant cells among the leukocytes in the small gummata, while Einhorn noted the presence of granular detritus, fat globules, few nuclei, nuclear fragments, and occasionally connective-tissue fibrils. The capsule, he says, is made up of scar tissue.

Fat was not demonstrable in these sections, but this does not imply that it is absent, for until the sections were examined microscopically the true condition of the specimen was not recognized, and since the tissue was not fixed in osmic acid, the fat was probably dissolved during preparation.

Incidentally it may be mentioned that the sections also showed a moderate amount of pigmentation near and around the central veins, where more or less congestion is present.

Sections taken from the fibrous mass at the junction of the hepatic and the cystic ducts are entirely composed of dense wavy fibrils of connective tissue containing many lymphoid cells principally diffused throughout the fibrous mass; occasionally they form mantles around the bloodvessels. The nodule contained no recognizable liver substance, nor were there any ducts found. Although not the usual site for gummata, neverthelesss, the fibrous mass was taken to be a retrocedent and cicatrized gumma. Adami refers to gummata occurring in the region of the gall-bladder, while Marchand, in his studies of syphilitic livers in infants, found cellular infiltration around the vessels at their entrance to the organ. Reference has already been made to the case reported by Lazarus-Barlow, who believed the occlusion of the hepatic duct was due to the organization of old gumma. In MacKenzie's case the cystic duct was so occluded that the bile could not be made to flow by pressure upon the gall-bladder. The miliary gummata in the present case are in all instances of recent

origin, and it is very difficult to believe that they are due to the same infection that gave rise to the gumma at the cystic and hepatic ducts. It is fairly well established that a second syphilitic infection may occur in the same individual, and this may account for the presence of the recently formed gummata. This view is suggested because sometimes miliary gummata of recent origin are found in the masses of old fibrous tissue which have degenerated and become necrotic just as the liver tissue or the reticulum of the organ in this case.

The greenish tinge of the liver, skin, conjunctiva, and other organs mentioned in the postmortem protocol can be explained by the fact that the bile-ducts are extensively involved by the fibrosis, and obstruction must have been present.

Fournier maintained that he never failed to find ascites accompanying syphilitic disease of the liver, while Trinkler says in some cases it is absent. This to a certain degree depends upon the involvement of the bloodvessels, especially its extent, or, as has been maintained by some authors, it is due to associated irritation or to actual inflammation of the peritoneum. The accumulated fluid found in the gall-bladder at autopsy was attributed to the supposed tuberculosis of the liver, with secondary involvement of the walls of the gall-bladder; sections of this organ show no conspicuous change in the wall and no gummata, and, therefore, the hydrops cystidis felleæ seems to have resulted from irritation incident to obstruction of the duct.

The time intervening between the infection and the development of the lesion in the liver has been much discussed. Adami states that in acquired syphilis of the liver we know very little about the effect upon the organ during the secondary stage, but, judging from the lesions seen in infants with the acquired form of the disease, there is a general intoxication which results in a catarrhal hepatitis. Hilton Fagge reports a case with a history of syphilitic rash, falling of hair, macular syphilides, jaundice, unconsciousness, and finally death. Although a microscopic examination of the sections of the liver was made, he says there were present only such changes as could be attributed to a general toxic condition of the organ. Cumston maintains that the liver is not affected until at least five years after the infection, but may become involved as late as ten or twenty years after.

February 9, 1905.

Proceedings

of the

Pathological Society of Philadelphia.

New Series, Vol. VIII. No. 5, 1905

TABLE OF CONTENTS.

Smith, Histologic Changes Encountered in the Thymus and Elsewhere in a Case of Congenital Hypotonia.—Rosenberger, A Study of the Mesenteric Glands in Their Relations to Tuberculosis.—Longcope, Tuberculosis of the Thoracic Duct and Acute Miliary Tuberculosis.—Alburger, Anthracosis of the Liver in Pulmonary Tuberculosis.

Histologic Changes Encountered in the Thymus and Elsewhere in a Case of Congenital Hypotonia.

By ALLEN J. SMITH, M.D.

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In a recent number of the *University of Pennsylvania Medical Bulletin*, January, 1905, Dr. William G. Spiller, after a brief review of our knowledge of the condition known as *myotonia congenita*, has given the clinical features and results of histologic study of central and peripheral nervous structures and muscles presented by a case under his charge in the University of Pennsylvania Hospital, adding thereto a *résumé* of the general findings at the autopsy conducted by Dr. A. F. Coca. At the time of publication of Dr. Spiller's article the histologic study of the visceral specimens obtained at the post-mortem examination had not been reached in the general laboratory, and, unfortunately, no note of the conditions discovered shortly afterward was had by him. With a view of adding what are possibly important data in relation to the affection the following additional features are offered supplementary to the studies outlined in Dr.

Spiller's article upon the case in hand, the first thus far definitely known to have come to the autopsy table.

While not excluding a possibility of the existence of the point of departure in the central nervous system (more particularly the anterior spinal horns), Oppenheim[1] inclines to regard the affection as rather one of the muscular system, resulting in arrest of muscular development; a conclusion supported by Spiller[2] who has failed to discover in the brain, cord, optic nerves, and peripheral nerves from both upper and lower extremities, any gross or minute change, but who notes in muscular tissue taken from the sole of the foot, from the calf of the leg, and from the back of the trunk that the fibres are hyaloid, 'their transverse striæ well preserved, longitudinal striations less distinct, the fibres small (particularly those from the foot and calf), and those from the foot notable "on account of the large amount of fatty connective tissue and on account of the considerable increase in the nuclei of the connective tissue."

For a full account of the clinical features of the case reference should be made to Spiller's article. The patient, a white male child, in its second year of age, was first seen by Dr. Spiller in May, 1904, was admitted to the University Hospital on July 15, 1904, and died August 5, 1904. Nothing of suspected import to the case was elicited in the family history. It was a full term baby; nothing abnormal in the labor. Nothing untoward was noted in the development of the child after birth, but when about five months old, because of an apparent apathy and inattentiveness to objects usually attractive to infants, the eyes were carefully examined and it was realized that almost complete blindness existed. The most notable feature of the case when first studied by Spiller (stated by the mother after close inquiry to have been present practically from birth) was a marked lack of muscular tone. With this existed absence of reflex movements. The child was never able to stand, to raise itself to a sitting posture, to hold any object in the hand, or to maintain a sitting position save when carefully balanced and then only for a few moments. The inferior members, which showed this flaccidity to a greater degree than the upper, could, without discomfort to the

[1] Monatsschrift f. Psychiatrie u. Neurologie, September, 1900. [2] Ibid.

child, be bent forward on the trunk and the foot curved about the neck; and the leg could be bent anteriorly at the knee so as to form an angle with the thigh. Voluntary movement was present but weak; the muscles responded to faradic stimulation. Death took place in a febrile attack of unknown nature, starting several days before death and reaching its maximum of 104° F. on the date of death.

The autopsy was performed the following morning by Dr. A. F. Coca, who noted the following gross features, referring the brain, cord, several peripheral nerves and muscle as above indicated to Dr. Spiller for special study:

Body of male white infant of fair development for its age; slight putrefactive discoloration evident over lower part of abdomen; rigor mortis absent and limbs flaccid as described in life; no postmortem lividity; no edema. Head large in proportion to body; eyes deeply sunken; pupils unequal (left, 2.5 mm.; right, 3.5 mm.). On preliminary incision moderate fatty panniculus; muscle substance pale, comparatively dry, notably flabby and rather poorly developed. Peritoneum smooth, no adhesions; omentum small, containing but little fat. Spleen weighed 12 to 15 grams, dark red in color; capsule free from adhesions, smooth and of normal thickness; organ of normal consistence; Malpighian bodies easily seen in cut section. Nothing abnormal noted in the gastrointestinal canal beyond the presence of a Meckel's diverticulum 4 cm. in length, situated 70 cm. above the ileocecal valve. The mesenteric lymph nodes were much enlarged, pale, some slightly reddened, fairly firm and not cheesy. The liver weighed 240 grams; was of normal consistence, mottled yellow and red in color, with smooth and transparent capsule, and without gross lesions in the cut substance; the gall-bladder normal, containing a small amount of light, greenish-yellow bile. The pancreas grossly normal; soft, and of light pink color. No gross changes recognized in the kidneys, ureters or bladder. In the thorax note is made of the normal appearance of the pleural membranes; absence of gross lesions of the lungs aside from slight hypostatic congestion of the dependent parts. The heart weighed 22 grams; the wall of the left ventricle measured 7 mm.; myocardium pale but firm; pericardium and endocardium normal throughout. Note was made of the absence of gross change in the thymus body.

For microscopic study in addition to the parts referred to Dr. Spiller, bits of tissue from the following parts were retained and in course of time prepared and examined: (*a*) Thymus gland; (*b*) heart, wall of left ventricle; (*c*) lung, from unindicated non-congested portion; (*d*) liver; (*e*) pancreas; (*f*) spleen; (*g*) mesenteric lymph node; (*h*) kidney; (*i*) wall of bladder. Of these parts the heart wall, pancreas, kidney and wall of the bladder show no recognized histologic changes; and the liver is practically normal beyond a slight fatty infiltration and a small degree of small round-cell infiltration about a few of the bile ducts (embryonic connective-tissue cells).

The thymus body shows marked interlobular sclerotic changes, the sclerotic tissue appearing as loosely arranged hyaline bundles, each of these sending large hyaline fibrous trabeculæ into the interior of the lobules, dividing the latter until it is difficult to determine the outlines of the original lobules. Within the lobules the reticular structures are much increased as well; and the arteries almost invariably show some degree of fibrous thickening of the adventitia, a few also showing well-marked intimal fibrosis with proliferation of the lining endothelial cells. The usual arrangement of the lobules into a denser peripheral and looser central area is not maintained, the peripheral zone, largely because of the prominence of the fibrosis, being if anything less lymphoid than the interior portion of the lobule. The lymphoid cells in themselves present no alterations, but a few mitotic nuclei were detected in them in different parts of the section. The most interesting feature of the section is the very large size and number of Hassall's corpuscles. These bodies with favorable light are in the larger instances recognizable by the unaided eye, some easily reaching 0.2 to 0.25 mm. in diameter. They occur indifferently toward the periphery or in the central portions of the lobule and often occupy a large proportion of its space. As a rule, they lie enclosed within thin but definite fibrous capsules, probably condensed reticular tissue of the surrounding lymphoid structures, each, as a rule, lying within a space probably the result of artefact, but they are generally attached at least on one side to the capsule. For the most part the larger examples are made up of several subordinate centres, around each of which the flat cells are concentrically packed, these subordinate ones fused together with the peripheral

cells enveloping the whole group. Often the centre of such a corpuscle selects a marked hematoxylin tint in a manner to suggest at least beginning calcification, the remainder of the corpuscle taking the eosin tint. Stained with carmine and subsequently submitted to the iron reaction with potassium ferrocyanide and hydrochloric acid a few of the corpuscles show a small amount of blue granular matter usually in the centre but in some instances scattered in the outer portion; and occasional granules of the Prussian blue are to be found in the lymphoid tissues of the general structure of the section. For the most part the concentrically packed cells show no trace of nuclear structure; but in many instances there are to be found on the outer portion of the corpuscle or lining the capsule of the space in which the corpuscle lies one or two layers of flat cells showing well-preserved nuclei; and occasionally in the centre of the body are a few cells preserving some nuclear appearances. In a few of the small bodies about the interior mass, usually poorly staining and hyaloid in appearance, are to be seen protoplasmic masses taking a light hematoxylin tinge and containing half a dozen or more nuclei, resembling ordinary giant cells or syncytia. There is no uniformity in the density of these Hassall's corpuscles, some being quite dense, hyaloid, and showing but faintly the concentric lines of separation of the cells composing them, while others are extremely loose with their scale-like cells more or less widely separated.

Here and there in the midst of the lymphoid cells and without definite separation from them are islets of endothelioid cells, each such islet showing in its section from two or three to perhaps a dozen of these cells, suggesting the "germ centres" seen in ordinary lymph follicles.

In the section of lung submitted for examination no abnormality of the pleura or of the general pulmonary tissue is to be recognized; but along the heavier fibrous septa of the structure are occasionally found collections of lymphoid cells, one of which in the section is perhaps a millimeter in diameter and easily seen with the unaided eye, the rest microscopic. These collections follow the type of ordinary lymph nodules, the larger one mentioned showing endothelial lined channels resembling sinuses and small islets of endothelioid cells reminding one of the germ centres of follicles.

In the spleen nothing of import is noted in the capsule or in the general splenic pulp, aside from moderate congestion of the latter. The trabeculæ are not thickened. Many of the vessel walls are unduly dense, sometimes actually hyaline; and some show distinct perivascular thickening from fibrosis. The Malpighian bodies are large, often in long sections they envelope the follicular arterioles for an unusual length, and a number show well-marked central endothelioid proliferation.

The mesenteric lymph nodes show on section a distinct excess of the lymph cells of the follicles and cords, the sinuses being practically occluded by them. No germinal centres are visible. The vessels are highly injected.

The above findings, fibrosis of the thymus with enlargement of the corpuscles of Hassall, endothelial proliferation in the thymus and in the Malpighian bodies of the spleen, arteriosclerosis noted in the thymus and in the spleen, the presence of lymph nodes in the lung and the proliferation of the lymphoid elements of the mesenteric lymph nodes, constitute undoubtedly interesting features of the case in hand. That they are an essential part or in any sense basic to the condition manifested in life by the muscular hypotonia can, of course, not be predicated from their discovery in this isolated case; but they unquestionably suggest the need for inspection along the same line in future investigations. *A priori*, from the theoretic view indicated by Oppenheim and confirmed by Spiller's positive findings in the present case, the muscular changes may be regarded at least tentatively as a definite feature of the affection. Our knowledge of the functions of the thymus and of its Hassall's corpuscles, usually looked upon as vestigial rather than as essential elements with active function, is too vague to permit anything beyond a mere surmise; but it is not inappropriate here to keep in mind the general idea that the thymus either by internal secretion or by destruction of untoward products of metabolism has an influence upon the development of all or of parts of the body either directly or through some action upon the trophic nervous power. One must further consider the possibility that back of all the changes described, muscular as well as the alterations of the thymus, there may exist some condition of autointoxication; and it is conceivable that there

might arise in the economy through faulty metabolism some material having stimulative influence upon the vascular and lymphatic endothelium, the proper lymphoid cells and upon the connective tissues of vascular walls and of the thymus itself, and at the same time capable of so interfering with the trophic nervous influence as to give origin to the muscular faults indicated above. There is, of course, no proof of such a suggestion, but the features narrated from the case in hand are not incompatible with the idea. It should be added here that, while at the time of autopsy the enlarged mesenteric lymph nodes were tentatively ascribed to tuberculosis, there was nothing in the gross features of the case, in the histologic findings or in special preparations made with a view to finding the bacilli, which in the least confirmed the supposition; and on the other hand, while it is quite possible to encounter changes of the type here indicated in the mesenteric nodes and in the spleen secondary to comparatively simple intestinal changes, there was nothing found in gross inspection of the intestines or in the histologic study of a small portion of the small intestine, fortunately retained by Dr. Spiller and studied subsequently to the above investigations, which would lead to the conclusion that the intestine was the seat of changes primary to these splenic and lymphatic proliferations.

From an anatomic standpoint the enlarged Hassall's corpuscles are of especial interest. Their size and appearance, with the outer layer or two of their cells alone preserving nuclear structure, suggest that these bodies are not to be accepted as mere vestigial structures, but rather as actually growing bodies developing by peripheral cell multiplication. The close similarity of some of the smaller bodies to some of the small bloodvessels with proliferated endothelium, the peculiar giant cells (much more commonly of connective tissue or endothelial origin than epithelial) found at the borders of some of the corpuscles, and the occasional discovery of iron in the interior of these bodies, would add some weight to the view long since suggested by Afanassieff[1] that these bodies are derived from proliferation of vascular endothelium. Not infrequently in the sections studied appearances are encountered suggesting the development of the

[1] Arch. f. mik. Anat., 1877, Bd. xiv.

bodies from such endothelioid islets as are noted as occurring in the midst of the lymphoid cells of the organ; and it seems quite possible that these areas should be regarded equally with the endovascular endothelium as capable of giving rise to the structures in question, these areas representing either "germ centres" or the proliferated endothelium of lymph spaces. Recent studies upon the development of the thymus and its corpuscles in guinea-pigs in the Biologic Laboratory of the University of Pennsylvania and communicated personally to the writer by Dr. E. C. Conklin, conclusively indicate that these bodies are not epithelial vestigia; that on the other hand they do not normally develop from the vascular endothelium, appearing at a period when bloodvessels are not to be distinguished in the thymus, but that they take their origin from certain large, often branched, connective-tissue elements found in the organ which are easily differentiated from the rest of its tissue by their staining reactions with Mallory's connective-tissue stain. *May* 25, 1905.

A Study of the Mesenteric Glands in Their Relations to Tuberculosis.

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This investigation involved a study of the mesenteric glands in 70 cases divided into two principal groups, the tuberculous and the non-tuberculous. The tuberculous group numbered 49, and included those in which one or more distinct tuberculous foci, great or small in extent, could be demonstrated somewhere in the body. The non-tuberculous group numbered 21, and included those in which it was impossible by gross examination to demonstrate in any part of the body a tuberculous lesion.

The mesenteric glands were placed under three headings: (1) the apparently normal, (2) the enlarged, (3) the tuberculous. The normal glands need no comment. Under the enlarged glands (a rather indefinite term), were included all those in which no changes

other than an increase in size and perhaps softening could be demonstrated. As the glands in infants and children are normally relatively large, they were not denominated as such unless the increase in size was marked. The tuberculous glands included all those which were grossly the seat of tuberculosis, whether tubercle bacilli could be found in spreads or not.

Of the 49 tuberculous cases, 6 were pulmonary tuberculosis with normal mesenteric glands; 1 was a case of pulmonary and intestinal tuberculosis with normal mesenteric glands; 7 were pulmonary tuberculosis with enlarged mesenteric glands; 9 were pulmonary and intestinal tuberculosis with enlarged mesenteric glands; 5 were pulmonary tuberculosis with tuberculous mesenteric glands; 14 were pulmonary and intestinal tuberculosis with tuberculous mesenteric glands; 5 were general miliary tuberculosis with enlarged mesenteric glands; 1 was a case of tuberculosis of the bronchial lymph nodes with enlarged mesenteric glands; and 1 was a case of primary intestinal tuberculosis with terminal general miliary tuberculosis and tuberculous mesenteric glands.

The mesenteric glands then were normal in 7, enlarged in 22, and tuberculous in 20 of the 49 cases in the tuberculous group. In nearly 60 per cent. the glands showed no gross evidence of tuberculosis. Of the 25 cases in which there were both pulmonary and intestinal lesions, 60 per cent. of the glands were tuberculous. Of the 18 cases in which there were pulmonary but no intestinal lesions, about 28 per cent. of the glands were tuberculous.

In all cases cover-glass spreads were made from the glands and examined for tubercle bacilli. Of the 49 cases of the tuberculous group, tubercle bacilli were found in 25 and could not be demonstrated in 24. The bacilli found possessed the morphologic and tinctorial properties of the human tubercle bacillus.

Of the 25 cases of the tuberculous group showing tubercle bacilli in spreads from the mesenteric glands, 1 was a case of pulmonary and intestinal tuberculosis with normal mesenteric glands; 2 were pulmonary tuberculosis with enlarged mesenteric glands, without intestinal lesions; 5 were pulmonary and intestinal tuberculosis with enlarged mesenteric glands; 5 were pulmonary tuberculosis with tuberculous mesenteric glands, without intestinal lesions; 11 were

pulmonary and intestinal tuberculosis with tuberculous mesenteric glands; while 1 was a case of primary intestinal tuberculosis with terminal miliary tuberculosis and tuberculous mesenteric glands.

Thus, 36 per cent. of the glands showing tubercle bacilli in spreads gave no gross evidence of tuberculosis.

Of the 24 cases of the tuberculous group not showing tubercle bacilli in spreads from the mesenteric glands, 6 were pulmonary tuberculosis with normal mesenteric glands; 4 were pulmonary tuberculosis with enlarged mesenteric glands; 5 were pulmonary and intestinal tuberculosis with enlarged mesenteric glands; 3 were pulmonary and intestinal tuberculosis with tuberculous mesenteric glands; 5 were general miliary tuberculosis with enlarged mesenteric glands; and 1 was a case of tuberculosis of the bronchial lymph nodes with enlarged mesenteric glands.

In this latter group of cases in which tubercle bacilli could not be demonstrated in spreads from the mesenteric glands, a further test of the tuberculous infectivity of the glands was made by stripping the capsules, macerating the pulp in bouillon and injecting 1 to 2 c.c. of this suspension into the peritoneal cavity of guinea-pigs. Nine of these animals died in from twenty-four to forty-eight hours after the injection, and nothing could be ascertained regarding possible tuberculosis of the glands used in injecting them. Of the remaining 15 pigs, 2 died in three and four weeks respectively, and 13 were killed in six weeks. Of these 13, 12 showed marked tuberculous lesions in the liver, spleen, lungs, and occasionally the peritoneum. In a number of these lesions, tubercle bacilli were demonstrated. The one pig failing to show tuberculosis was injected from a case in which the only tuberculous lesion was an old healed scar at the apex of one lung.

Thus, 87.5 per cent. of the 24 cases of the tuberculous group not showing tubercle bacilli in spreads gave no gross evidence of tuberculosis, while the infectivity of these glands on animals was shown in 15 out of 16, or 93.75 per cent. of cases. Or, taking the whole tuberculous group of 49 cases, and ignoring the 9 cases in which the inoculated pigs died early, 39 out of 40 cases or over 97 per cent. gave evidence of tuberculosis, though in 60 per cent. of cases the glands gave no gross evidence of the disease.

The relations between the finding of tubercle bacilli in spreads from the glands and evident tuberculous lesions in the 49 cases are conveniently noted by observing that there were 6 cases of pulmonary tuberculosis with normal mesenteric glands, none of which showed tubercle bacilli; 1 case of pulmonary and intestinal tuberculosis with normal mesenteric glands, in which no tubercle bacilli were found; 7 of pulmonary tuberculosis with enlarged mesenteric glands, 3 showing and 4 not showing tubercle bacilli; 9 of pulmonary and intestinal tuberculosis with enlarged mesenteric glands, 4 showing and 5 not showing tubercle bacilli; 5 of pulmonary tuberculosis with tuberculous mesenteric glands, all of which showed tubercle bacilli; 14 of pulmonary and intestinal tuberculosis with tuberculous mesenteric glands, 11 showing and 3 not showing tubercle bacilli; 5 of general miliary tuberculosis with enlarged mesenteric glands, none of which exhibited tubercle bacilli; 1 of tuberculosis of the bronchial lymph nodes with enlarged mesenteric glands, tubercle bacilli not being demonstrable; and 1 of primary intestinal tuberculosis, with terminal general miliary tuberculosis, and tuberculous mesenteric glands, in which tubercle bacilli were found.

The non-tuberculous group, in which it was impossible to demonstrate by gross examination tuberculous lesions in any part of the body, included 21 cases. These died from a variety of causes, among which were diseases especially likely to cause enlargement of the mesenteric glands, such as typhoid fever and bacillary dysentery. The glands were apparently normal in 6 and enlarged in 15 instances. Of the 21 cases, 10 were children. In 9 of these 10 the glands were enlarged. In the 11 adult cases there were 6 instances of glandular enlargement. As far as the results here obtained indicate, however, the size of the glands is probably of little importance; and the enlargement in so many cases in children was due to the fact that most of them died of ileocolitis.

The mesenteric glands in the non-tuberculous group were all examined for tubercle bacilli, but the spreads gave negative results.

The glands from each case were then macerated in bouillon and inoculated into guinea-pigs, as in certain of the tuberculous cases. Of the pigs injected, 6 died within forty-eight hours, and these cases were not considered. The 15 animals that survived were killed

six weeks after the dates of inoculation. Six of the pigs showed distinct tuberculous lesions in the liver, spleen, and lungs; 8 gave negative results; and 1 was doubtful, exhibiting only a few pinhead-sized foci in the liver. This last case was ignored.

Thus in a little over 40 per cent. of cases the mesenteric glands of the non-tuberculous group were shown to be capable of producing tuberculous lesions in guinea-pigs. Of the 14 cases in which the test was satisfactorily carried out, 9 were adults and 5 were children. Of the adults, 4 gave positive and 5 negative results. Of the children, 2 gave positive and 3 negative results. The division is thus fairly even. That enlargement of the glands alone bore little relation to the results obtained is shown by the facts that in the cases in children the glands were enlarged in all 5 instances, 2 giving positive and 3 negative results; and that in the adult cases the glands were normal in 4 and enlarged in 5 instances, 2 of the former giving positive and 2 negative results, while 2 of the latter gave positive and 3 negative results. The ages of the children are of some interest, as is also the fact that all of them were hospital cases and bottle-fed. The two children giving positive results were two and nine months old respectively, and died of ileocolitis. The three children giving negative results were one, two, and nine months old respectively. It is also worthy of note that 2 cases of typhoid fever in adults gave negative results.

Was the tuberculous infectivity of the lymph glands of the mesentery, as shown in 97 per cent. of the tuberculous and 40 per cent. of the non-tuberculous cases, peculiar to them? Or, was it shared by the other lymph nodes of the body? Were the parenchymatous organs also involved? An attempt was made to answer these questions by a few experiments along lines similar to those followed in the study of the mesenteric glands.

The enlarged axillary glands from a case of chronic pulmonary tuberculosis were tested for tuberculosis by examination of spreads and inoculation of a guinea-pig. The spreads showed no tubercle bacilli, but the pig developed marked tuberculous lesions of the spleen, liver, lung, and peritoneum.

The apparently normal inguinal glands from a case of general miliary tuberculosis in a ten months infant were tested in the same

way. The spreads showed no tubercle bacilli, but the pig developed tuberculosis in the spleen and liver.

The slightly enlarged inguinal glands obtained from an adult without the slightest gross evidences of tuberculosis anywhere in the body were inoculated into a guinea-pig. The animal was killed in six weeks and showed marked tuberculous lesions of the liver, spleen, and lung.

Portions of spleen, liver, and kidney obtained from a case of chronic pulmonary tuberculosis, but showing no gross evidence of tuberculosis themselves, were inoculated into guinea-pigs. All of the animals developed very marked tuberculous lesions in the spleen, liver, and lungs.

Portions of spleen, liver, and kidney were likewise obtained from a case showing no tuberculous lesions in any part of the body and used for similar inoculations. The pigs injected were killed at the end of six weeks and were found to be free from tuberculosis.

These few cases do not warrant positive conclusions, but they suggest rather strongly that the tuberculous infectivity of the mesenteric glands is common to gland groups in other parts of the body. The importance of this point lies in the logic supposition that involvement of the mesenteric group alone would mean infection from the intestines, while general involvement of the lymph nodes throughout the body would indicate hematogenic infection. The results obtained from inoculations with portions of spleen, liver, and kidney also offer the suggestion that, while the lymph glands throughout the body often harbor tuberculous material in the tuberculous and perhaps in the non-tuberculous, the parenchymatous organs are involved only when tuberculous lesions are present somewhere in the body. The evidence on this point, however, is too meagre for the suggestion to be of any value without further studies.

The extent of the lesions found in the infected pigs is of some interest. A few pigs were inoculated with distinctly tuberculous glands of the mesentery in which tubercle bacilli had been demonstrated in spreads; these died in from three to four weeks with very extensive lesions. The pigs inoculated with glands from tuberculous subjects, in which, however, no tubercle bacilli had been demonstrated, were killed at the end of six weeks (with two exceptions),

and showed lesions less marked than the preceding animals. The pigs developing tuberculous lesions after inoculation from non-tuberculous cases showed, on the whole, the least extensive lesions. The pigs inoculated from the inguinal and axillary glands exhibited quite marked lesions. The animals inoculated with spleen, liver, and kidney of the tuberculous case showed the most extensive lesions of all. Except in the cases where the pigs were infected with glands showing tubercle bacilli, and with the spleen, liver, and kidney of the tuberculous case, the animals gained weight progressively, contrary to what would be expected.

Controls were furnished all through the investigation by the pigs dying of the peritoneal injection within forty-eight hours. These numbered 15. In none of them were tuberculous lesions found.

Conclusions.—1. In all cases of active tuberculosis and in almost all cases of inactive tuberculosis the mesenteric glands are capable of infecting guinea-pigs with tuberculosis.

2. The mesenteric glands in these cases may or may not show gross evidence of tuberculosis or tubercle bacilli in spreads; the result of such a search is not distinctive as far as the production of tuberculosis is concerned.

3. The mesenteric glands in a certain percentage of cases that show no tuberculous lesions in any part of the body produce tuberculosis when inoculated. In the present study the percentage was about 40.

4. The tuberculous infectivity of the mesenteric glands is probably shared by the other groups of lymph nodes throughout the body.

The material used in the experiments was obtained from the Henry Phipps Institute by the writer during his service as pathologist to that institution, from the Philadelphia Hospital, and from private cases.

May 11, 1905.

Tuberculosis of the Thoracic Duct and Acute Miliary Tuberculosis.

By WARFIELD T. LONGCOPE, M.D.

(From the Ayer Clinical Laboratory, Pennsylvania Hospital.)

Tuberculosis of the thoracic duct has been recognized for over a hundred years. In 1798 the condition was discovered accidentally by Astley Cooper,[1] who described the lesions quite accurately and, moreover, interpreted his findings correctly, inasmuch as he considered that the great lymphatic vessel was the seat of scrofulous disease. Among the early writers Andral[2] is also credited by some with having described the same condition, but his notes are so vague that the correctness of the assumption is doubtful. It was, however, Ponfick[3] who really first drew special attention to thoracic duct tuberculosis and emphasized its connection with acute miliary tuberculosis, though he did not consider it as the cause of the generalized process. His original communications were made in 1877 and during the next year Weigert[4] reported his cases of vein tuberculosis, and announced his conception of the origin and pathogenesis of acute miliary tuberculosis. In 13 such cases he found foci of tuberculosis in the veins in 10, and of the thoracic duct in 2. From the nodules in the veins and in the thoracic duct he believed that the poison (this was prior to the discovery of the tubercle bacillus) was swept into the general circulation and thereby gave rise to the generalized acute process. According to Weigert, before a focus in a vein or lymph channel can be considered as the point of origin of the acute process at least four conditions must be fulfilled.

1. The tubercle in the wall of the vein or duct must be older than the miliary nodules scattered through the organs of the body.

2. The tubercle must be situated in a vein or large lymph vessel which is patent.

[1] Medical Records and Researches, 1798, vol. i. p. 86.

[2] Arch. gén. de méd., 1824, t. vi. p. 508.

[3] Berliner klin. Wochenschrift, 1877, No. 46, p. 673.

[4] 51 Naturfor. Versammlung, 1878; quoted from Virch. Arch., 1882, Band lxxxviii. p. 307.

3. The poison must reach the surface of the nodule—*i. e.*, communicate with the lumen of the vessel, a condition which is usually if not always satisfied in lesions of the thoracic duct.

4. The tubercle must not be situated in the portal vein.

Following Weigert's original work many investigators published observations which upheld and confirmed his doctrines. Not only were the tuberculous nodules of veins described in connection with general acute tuberculosis, but thoracic duct tuberculosis in which we are especially interested was noted.

Stilling,[1] in 1882, found tuberculosis of the thoracic duct in 5 of 18 cases of acute miliary tuberculosis, while Meissels,[2] in 1884, published the descriptions of 8 cases of acute miliary tuberculosis, in some of which tuberculosis of the thoracic duct occurred. In the same year Koch,[3] in his splendid work on tuberculosis, reports 11 cases of acute miliary tuberculosis, in 2 of which he mentions an involvement of the thoracic duct. Koch, of course, first demonstrated the presence of tubercle bacilli in the lesions of the veins and lymph channel and pointed to the actual dessemination of bacilli, the poison of Weigert, by way of the general circulation to the various organs of the body. Subsequently Weigert,[4] in his own specimens, confirmed Koch's work regarding the presence of bacilli in the nodules in the veins and thoracic duct.

Later, Brasch,[5] in a study of 24 cases of miliary tuberculosis, mentions an examination of the thoracic duct in 17 instances, and 9 times tuberculosis was discovered in this vessel. In 6 instances the tuberculosis was caseous in type. He emphasizes the relationship between involvement of the serous cavities and of the duct and concludes that the infection is carried to the duct from the peritoneum and pleuræ and not through the lymph nodes.

Hanau,[6] Sigg,[7] Helbing[8] and others have subsequently reported

[1] Virch. Arch., 1882, Band lxxxviii. p. 111.

[2] Wiener med. Wochenschrift, 1884, No. 30, p. 50.

[3] Mit. aus der Kaiserlich. Gesundheitsamte, 1884, Band ii. p. 24.

[4] Deutsche med. Wochenschrift, 1883, No. 24, p. 349.

[5] Diss., Heidelberg, 1886.

[6] Virch. Arch., 1887, Band cviii. p. 221.

[7] Quoted from Benda.

[8] Verhandl. d. Berl. med. Gesellschaft, 1889, Bd. xxx., Heft 2, p. 153.

cases of thoracic duct infection, while more recently Benda[1] has called particular attention to the condition. In a very large proportion of cases of general miliary tuberculosis, 12 out of 19, he found tuberculous disease of the thoracic duct and believes the localization of the process in this situation more than in any other gives rise to acute miliary tuberculosis. Benda considers that the primary infection of the vessel, whether it be vein, artery, or thoracic duct, attacks the intima. The process arises by a deposition of tubercle bacilli upon the intima of the vessel. Naturally this view has been frequently opposed.

Weigert's work and that of his followers has been criticised and his views strenuously contested by Wild.[2] Though not denying the occasional occurrence of macroscopic lesions in the veins and thoracic duct, Wild explains the origin of acute miliary tuberculosis differently from Weigert. He does not believe that the general process arises from an overwhelming invasion of the blood by tubercle bacilli liberated from a single focus of disease situated in a vein or the thoracic duct. In his conception the point of entry of the bacilli into the blood stream is hidden and obscure. By undiscoverable routes the bacteria enter the circulation in small numbers, and either here or in the organs multiply to produce the general infection. Though Wild is upheld in his views by Ribbert,[3] whose pupil he is, his work has not been generally confirmed and his following is small. Weigert[4] naturally confutes Wild's conclusions at every step.

From a short review of the literature it will be seen that more and more importance is being attached to tuberculosis of the thoracic duct as a point of origin for the general acute form of tuberculosis, while the lesions in the veins, particularly the pulmonary veins, which at first received so much attention, are now becoming of secondary importance. Silbergleit,[5] however, in a recent discussion of the subject, describes only 5 cases of duct infection among 23 well-studied cases of general acute miliary tuberculosis, though either vein or duct tuberculosis occurred in 95.6 per cent. of the total number.

[1] Ibid., p. 259.
[2] Virch. Arch., 1897, Band cxlix. p. 65.
[3] Deutsche med. Wochenschrift, 1897, No. 53, p. 841.
[4] Deutsche med. Wochenschrift, 1897, Nos. 48 and 49, pp. 761 and 780.
[5] Virch. Arch., 1905, Band lxxix. p. 283.

It may be said, however, that to exclude a lesion in the thoracic duct the vessel must be dissected from the receptaculum chyli to its entrance into the left subclavian vein, since in certain cases only a solitary tuberculous nodule may be found in its extreme upper portion.

In 25 cases of tuberculosis in which the process was more or less generalized, especial attention was paid to a study of the thoracic duct as a possible point of origin for the generalized process.

Eighteen of these cases occurred at the Pennsylvania Hospital and 7 at the Johns Hopkins Hospital. For this latter series I am greatly indebted to Dr. Wm. G. MacCallum, who placed the records of the autopsies at my disposal. The dissections of the ducts in most of the cases from the Johns Hopkins Hospital were made by Dr. Eugene Opie.

Of these cases 17 were typical instances of generalized acute miliary tuberculosis, where minute tubercles were scattered in enormous numbers through most of the organs of the body. Where histories could be obtained the course of the disease was rapid, lasting usually from two to twelve weeks. The thoracic duct in 12 of the 17 cases showed a more or less extensive tuberculosis, usually with caseous nodules, while in one instance, though there was no tuberculosis of the wall of the vessel, many tubercle bacilli were found in smears from the duct lymph. In 1 of the 4 remaining cases in which the duct was normal there was a primary tuberculosis of one epididymis and testicle with organized thrombi in the vesical veins, containing caseous masses and tubercles.

In six instances the generalized process was subacute or chronic. Large tubercles or caseous masses were scattered in small numbers through the various organs, while during life the course of the disease was protracted, lasting from three to nine months. In only 2 of the cases was there a tuberculosis of the thoracic duct. In both instances the tubercles were small and occurred sparingly, but in 1 a few tubercle bacilli were found in smears from the fluid of the duct.

Finally, in two instances the tuberculosis was of a chronic type and confined to the lungs and peritoneum. In both of these cases the thoracic duct was normal.

It is difficult to draw a line between the cases of acute and subacute

generalized tuberculosis, but between the extremes of the two types a distinction can certainly be made. The cases with which we had to deal were fortunately distinctive. Of the 23 cases of generalized tuberculosis 15, or over 65 per cent., showed tuberculosis of the thoracic duct, or, as in one instance, tubercle bacilli in the lymph from the duct. Of the acute cases in over 76 per cent. the duct was affected.

The type of lesion in the duct varied considerably. Sometimes there was a single large caseous nodule usually near the receptaculum or about the arch of the aorta with small tubercles over the intima of the vessel above and below it. Sometimes several caseous nodules were scattered through the duct, while occasionally the walls of the lymphatics were simply seeded with small tubercles. In every instance the lymph nodes of the mesentery, retroperitoneum, posterior mediastinum, or bronchial regions were the seat of a chronic tuberculosis. At times several groups of glands were affected, but more often only one group and rarely only one or two glands, as in Case VII.

Often the lesion in the duct appeared almost as old as that in the neighboring lymph node and was in close association with it, though a direct extension of the process from the gland to the wall of the duct was never seen. In at least two instances the caseation of a small group of lymph nodes and of the thoracic duct wall were the only foci of chronic disease which could be found in the body.

This intimate association between the lesions of the lymph nodes and of the duct which existed so often leads one to suppose that the infection travels directly from the lymph nodes through the lymphatics to the thoracic duct. It is well known, through the experiments of Nicolas and Descos,[1] Arloing,[2] Ravenel[3] and others that tubercle bacilli when fed to dogs may pass directly through the intestinal wall without producing perceptible lesions, travel to the mesenteric lymph nodes and rapidly enter the thoracic duct, where they may be demonstrated soon after the feeding. The method of infection ascending from foci of disease in the abdomen, or travelling from lymph nodes elsewhere in the body through the blood to the lungs

[1] Cent. f. Bact. u. Parasit., 1902, Band xxxii. p. 306.
[2] Presse méd., 1903, No. 29, tome i. p. 298.
[3] Journal of Medical Research, 1903, vol. x. p. 460.

has recently received much study. Harbitz[1] has lately reviewed the literature upon this subject.

Apparently the same series of events takes place in these cases of thoracic duct infection. In a certain number of instances tubercle bacilli are carried to the thoracic duct from adjacent tuberculous lymph nodes. Here they lodge and produce a localized subacute or chronic lesion. Sooner or later this nodule breaks down and enormous numbers of tubercle bacilli, as may be demonstrated by smears of the lymph, are liberated and swept by the lymph into the general circulation, producing an acute and rapidly fatal general tuberculosis. Even if a large tributary to the duct is the seat of a caseous tuberculosis the same series of events may follow and, as in one of our series of cases, tubercle bacilli would be swept into the lymph of the duct without of necessity producing changes in its walls; or, as has been frequently noted, only give rise to a miliary tuberculosis of the duct itself. It has frequently been shown that neither during life nor at autopsy can large numbers of tubercle bacilli be demonstrated in smears from the blood, so that the mere presence of large numbers of tubercle bacilli in the lymph from the thoracic duct suggests that they are disseminated from a reservoir near by.

Of special interest are the cases of subacute generalized tuberculosis with lesions in the duct. In such cases it seems probable that from tuberculous lymph nodes, tributaries to the duct and small foci of tuberculosis in the duct itself, a few tubercle bacilli may, from time to time, be swept by the lymph into the circulation and scattered to different parts of the body, producing a chronic general infection instead of the rapidly overwhelming type of infection.

Our series of cases suggest, therefore, that the thoracic duct is of great importance as a channel for the spread of tubercle bacilli through the body from the various groups of lymph nodes. Undoubtedly tuberculosis of the veins and arteries is also to be reckoned as a factor in the rapid dissemination of tubercle bacilli through the body, but is subsidiary in importance to tuberculosis of the thoracic duct and its tributaries. From a study of these cases the following conclusions may be drawn:

[1] Journal of Infectious Diseases, 1905, vol. ii. p. 143.

Tuberculosis of the thoracic duct is of great frequency in cases of acute generalized tuberculosis. The lesions in the duct from which tubercle bacilli are swept in great numbers through the lymph to the general circulation form the starting point for the generalized acute process. In certain cases of acute generalized tuberculosis, tubercle bacilli may be found in the lymph from the duct, though the duct itself is not the seat of tuberculosis. In a small percentage of cases of subacute generalized tuberculosis the duct may also be affected. *May* 11, 1905.

Anthracosis of the Liver in Pulmonary Tuberculosis.

By H. R. ALBURGER, M.D.

Pigmentation of the liver with particles of carbon, that come through the lungs and are the result of inhalation of coal-dust and smoke, is a fairly rare condition, as evidenced by the fact that in only 1 case out of 400 autopsies at the Philadelphia and University Hospitals was it found. Cases have, however, been reported by Soyka, Arnold, Weigert, Welch and others.

In the vast majority of cases there is merely a collection of granules of pigment in the interlobular connective tissue of the liver; this may be recognized as identical with that commonly found in the lungs, both by its morphology and by its resistance to strong acids and alkalies. In the situation mentioned, it usually causes no structural changes in the connective tissue in which it lies or in the surrounding parenchymatous cells, but in one extremely unusual and interesting example, reported by Welch, there was a marked increase of the connective tissue wherever the pigment was found, together with necrosis of the adjacent liver cells, due to the direct irritation of the foreign material or of some irritant or toxic substance brought with it to its seat of deposition. The cirrhosis was such a marked feature in this case that Welch has given it the name of cirrhosis hepatis anthracotica.

How this pigment gains entrance to the liver is a point of much interest. The bronchial lymph glands normally act as perfect filters

for the lymph coming to them from the lungs, but, as shown by Weigert, when they are the seat of destructive inflammation or are involved in adhesions due to surrounding inflammatory processes, favorable conditions are offered for the entrance of their contained pigment into the general circulation by softening and rupture into neighboring bloodvessels. Should such rupture take place, we should expect to find the carbon deposited in various organs, chiefly the spleen, liver, and kidneys; this proves to be frequently the case in the spleen, which is much more often the seat of anthracosis than any other of the abdominal viscera, the liver much less frequently and the kidneys least of all. Another possible channel through which the pigment could reach the liver is the lymphatic system, although this seems much less likely than through the blood stream, because of the numerous lymph nodes which intervene between it and the lungs, all acting as filters, and also because of mechanical difficulties. Still another mode of entrance is the portal circulation in case particles of carbon have been swallowed. Under such conditions we would expect to find a deposit in the walls of the intestine and the mesenteric lymph nodes rather than in the liver.

Granting, then, that the most probable manner in which the pigment gains entrance to the liver is through the general circulation through softening and rupture of the bronchial lymph nodes into adjacent blood paths, tuberculosis certainly produces most frequently the lesions that are favorable to such rupture or erosion. Arnold has pointed out the association of emphysema of the lungs with anthracosis of the liver, but it would seem that tuberculosis offers still more favorable conditions. Welch's case would have been an extremely good one to study in this connection, on account of the large amount of pigment, so much being present that it could be seen with the unaided eye in the gross specimen, showing as small black specks and streaks, both through the capsule and in the cut section. Unfortunately, the autopsy was not complete, and the thorax was not opened, thus making it impossible to do more than surmise the condition of the bronchial lymphatics.

The case to be reported showed a moderate degree of anthracosis of the liver, with some connective-tissue increase. The tissues were obtained from an autopsy performed at the Philadelphia Hospital.

The patient, M. W., a female, aged fifty-five years, had been sent to the hospital suffering from inoperable carcinoma of the uterus. This condition was found at autopsy, together with extension of the cancer to the appendages and postperitoneal lymphatics. The lungs showed chronic tuberculosis.

The autopsy notes were as follows: Pleuræ: Left pleura is adherent by fibrous bands over the outer aspect and about the apex. Right pleura is even more adherent about the apex and posteriorly. Left lung weighs 500 grams, is fairly voluminous; the borders slightly blunt; shows a moderate amount of anthracosis; somewhat pale anteriorly and deeply congested posteriorly, the pleural surface showing marked fibroid adhesions about the apex. On cut section the entire lower lobe and a great portion of the upper lobe show diminished crepitation, and on slight pressure exude a light-colored, frothy fluid, together with some blood. The bronchi and bronchioles exude also a clear, whitish fluid. At the apex there is an area of consolidation of mottled color, containing many calcareous nodules and involving particularly the peribronchial lung tissue; several similar small calcareous nodules are found scattered through the lung, and at the margin of the posterior inferior surface of the upper lobe is a small area of peribronchial consolidation, apparently cheesy, about 2 cm. in diameter.

Right lung weighs 590 grams, is fairly large; similar externally and internally to the left. On cut section shows much frothy fluid with slightly more blood than its fellow. At the apex is an area about 4 cm. in diameter of complete consolidation, yellow in color, with numerous hard nodules. No notes were made upon the bronchial lymph nodes, but from the condition of the lungs it is probable that they were more or less involved by the tuberculous process.

The kidneys were the seat of advanced chronic interstitial nephritis, together with severe amyloid infiltration. The spleen showed amyloid infiltration and a small amount of carbon pigment about some of the larger vessels.

The liver weighed 1400 grams; extended four fingers' breadth below the costal margin as a result of prolongation and flattening of the right lobe by pressure of tight clothing; and showed a shallow, transverse groove across the prolonged lobe, with thickening of the

capsule in the depressed area. The cut section presented a red surface with indistinct markings.

Microscopic examination showed the following features: The capsule of the organ is somewhat thickened, as is the interlobular connective tissue throughout the section, the thickening being due to an increase of connective tissue of young growing type; in this new tissue surrounding the bloodvessels we find accumulations of black carbon granules of irregular size and shape. These granules are identical in every particular with those usually found in the lungs and bronchial lymphatics. The liver cells throughout the section are somewhat swollen and decidedly indistinct, and the outlines of the cells not clear. The capillaries between the cells are filled with a faintly staining granular material. Some of the nuclei of the hepatic cells are large and swollen; others are shrivelled. In some places about the hepatic artery in Glisson's capsule we find a small amount of a hyaline substance, probably amyloid. With high magnification we find that the distribution of the pigment is much more general than is shown with lower powers; it is found in all portions of the lobule, even about the central vein, and is seen in the endothelial cells of the capillary walls, which are for the most part greatly swollen. A marked excess of polymorphonuclear leukocytes is also noted, both in the interlobular connective tissues where most of the carbon lies, and in the intralobular capillaries generally. *May* 11, 1905.

Proceedings

of the

Pathological Society of Philadelphia.

New Series, Vol. VIII. No. 6, 1905

TABLE OF CONTENTS.

Robinson, The Role of the Typhoid Bacillus in the Pulmonary Complications of Typhoid Fever.—Smith, Veeder, Tapeworm from Python Moluris.—Schamberg, Hirschler, Epithelioma of the Forehead having its Origin in a Papillary Nevus.—McReynolds, Interstitial Fibromyoma Complicating Pregnancy.

The Role of the Typhoid Bacillus in the Pulmonary Complications of Typhoid Fever.

By G. CANBY ROBINSON, M.D.

(From the Ayer Clinical Laboratory, Pennsylvania Hospital).

The fact that typhoid bacilli are not infrequently found in the lungs during an attack of typhoid fever is well established, but the effect of their presence is still uncertain. Artaud in 1885 was the first to mention the possibility of pulmonary invasion by typhoid bacilli, and he described typhoid-like bacilli in the lungs of two typhoidal patients dying of pulmonary apoplexy. According to Curschmann, lungs, the seat of gangrene, hypostatic splenization, or even lobar pneumonia due to the pneumococcus, undoubtedly may be invaded by typhoid bacilli. When one considers the constancy with which the typhoid bacillus enters the general circulation, and also that the organism has been obtained by a number of observers (Polguère, Montier, Roque, and Bancel) from lungs in a state of congestion only, then it is clear that the organism quite regularly enters the lungs during typhoid fever. Roque and Bancel obtained the bacillus six times in sixteen attempts by lung puncture during life from cases showing only bronchitis or pulmonary congestion. They think that the typhoid bacillus is present in greater numbers

in the pulmonary than in the systemic circulation and plays an important role in pulmonary complications of typhoid fever.

Although the organism has been recovered repeatedly from the lung, there are in the literature but few cases in which the typhoid bacillus seems surely to have produced a definite pulmonary lesion.

Several observations have been made recently at the Pennsylvania Hospital which throw some light upon the significance of the typhoid bacillus in pulmonary complications of typhoid fever.

CASE I.—N. B., male, white, aged twenty-two years, laborer, entered the Pennsylvania Hospital (No. 1594) August 19, 1902, service of Dr. Stengel. Patient is an Italian, speaking no English, so no history can be obtained. Temperature 103.2°, pulse 80, respiration 28. The patient is a well-built, well-nourished man; tongue coated; heart sounds are clear and distinct; lungs are everywhere resonant and the breath sounds are clear; liver not palpable; spleen is palpable. Abdomen is round and well formed. No tenderness is elicited. There are a few isolated rose-colored spots over the abdomen. Leukocytes, 18co. Typhoid bacilli agglutinated by patient's blood serum.

Patient remained in fairly good condition until September 16, when, after having had a slight cough and a slightly blood-streaked sputum for several days, he developed excessive cough, dyspnea, and hemorrhagic expectoration. The sputum is now almost pure blood and every effort to move produces a severe coughing spell. Such examination as can be made discloses subcrepitant and occasional piping rales on the right side. There is some impairment of resonance at the right base posteriorly. Few rales over left side. Heart sounds clear. Temperature rose to 104.6°, dropped in six hours to 98°, then rose on the next day to 105°.

September 17th. Loud, high-pitched squeak, systolic in time and without diastolic element, is heard in the region of the apex of the heart. A few pleural friction sounds can also be heard. Temperature irregular, ranging from 105° to 97°.

23d. Patient had a chill lasting several hours, after which he became steadily worse and died on September 24th.

Autopsy (No. 299) by Dr. Longcope.

Anatomic Diagnosis. Typhoid fever, healing ulcers of the ileum and cecum; thrombosis of branch of right pulmonary artery; abscess of right lung; acute fibrinous pleurisy; acute bronchopneumonia; acute splenic tumor; swelling of mesenteric lymph glands, parenchymatous degeneration of liver and kidneys, and infarct of right kidney.

An abstract from the autopsy notes is as follows: "The right lung is found to be bound to the pleura by fresh fibrinous adhesions, and in separating it from the parietal pleura a cavity is opened from which there escapes gas and a large quantity of dirty yellowish brown pus. The right lung is large and its lobes are bound together by old fibrous adhesions and by a fresh fibrinous exudate. The pleura over the anterior portion of the upper lobe and margin of the middle lobe is smooth and glistening, but posterior to this the surface of the lung is covered with a fine fibrous exudate, sprinkled here and there with small hemorrhages. The entire posterior portion of the lower lobe is found to be converted into an abscess cavity which measures 9 cm. in length and 5 cm. in breadth. This cavity has been opened in removing the lung from the body. The inner walls of the abscess are covered with a grayish-green necrotic material and along the walls can be seen irregular projections and villous-like processes. The walls are here and there ribbed with cords of tissue similar to the projections. Covering the lung about the cavity there is a heavy creamy fibrinous exudate which is sometimes 2 cm. in thickness.

"On sectioning the anterior portion of the lung numerous reddish-gray ill-defined areas of bronchopneumonic consolidation are found. In the posterior portion of the lung the cut surface is smooth, reddish gray and soggy and the tissue completely consolidated. The main artery leading to the lower lobe is plugged by a firm red and gray thrombus. The large bronchi can be followed directly into the abscess cavity, where they sometimes open and are sometimes covered with fibrin and pus. The thrombus can be followed down many branches of the artery to the abscess cavity, and the ends of the vessels are found to form the villous processes described in the wall of the abscess. The bronchi at the root are filled with blood and mucus.

"The left lung is voluminous. Most of the surface is covered by old fibrous adhesions. The entire lung is semisolid and feels as if filled with firm, irregular nodules. The cut surface shows dark-red

hemorrhagic consolidations which stand up above the surface and present a striking contrast to the pale crepitant intervening lung tissue. The consolidations are numerous, large, and confluent posteriorly, but anteriorly they are more sparsely scattered and smaller. Frequently the hemorrhagic nodules have a yellow center. The vessels are free from thrombi. The bronchi are injected and contain mucus.

"In the ileum about 80 cm. from the ileocecal valve a large, slightly swollen Peyer's patch is found, showing a rounded ulceration 0.5 cm. in diameter at its lower end. Nearing the cecum other ulcers are found, most of which are small and have clean bases. Some are partially covered with irregular extensions of the mucosa over the surface. The margins of some of the larger ulcers are deeply injected and irregular, but usually they are smooth and rounded. A few small ulcers are found in the cecum, but otherwise the large intestine shows no change.

"The spleen is much enlarged and soft. The mesenteric glands, many of which are the size of almonds, are swollen and injected.

"Iliac vessels free from thrombi."

The condition of the other organs is unimportant.

Microscopic Examination. (Zenker's fluid, paraffin, hematoxylin, and eosin.)

In all sections of the lungs an extensive bronchopneumonia is found principally of a desquamative type. Many alveoli are filled with desquamated epithelial cells, only a few of which are phagocytes. Elsewhere coagulated serum fills the alveoli either alone or together with desquamated epithelial cells, and a few polymorphonuclear leukocytes and red blood corpuscles. In certain foci, especially about the bronchioles, a characteristic exudate of fibrin and leukocytes extends in the alveoli, and sometimes in these areas there are hemorrhages covering the space of several alveoli and destroying the alveolar walls. The center of such foci is usually formed by a bronchus filled with fibrin, leukocytes, and nuclear fragments. The epithelium of the bronchi is desquamated and often the exudate is attached to the wall. The areas of bronchopneumonia appear to surround and extend from the bronchioles.

Sections stained by the Gram-Weigert method fail to show any bacteria. Sections stained with Loeffler's methylene blue (Flexner's method for typhoid bacilli in tissues) show collections of well-stained rod-like bodies, which in places, especially where polymorphonuclear leukocytes are most numerous, are formed into rather loose, well-defined masses.

The wall of the abscess is composed entirely of a mass of necrotic material, leukocytes, fibrin, and nuclear fragments. Directly beneath this exudate the bloodvessels are seen to be much engorged, and masses of red blood cells, closely packed and scattered through the tissue, are present. The blood and deeper portion of the exudate show beginning organization. The lung beneath shows extensive desquamation of epithelial cells with here and there areas of exudative pneumonia.

A section stained by Loeffler's methylene blue shows large numbers of typical small rod-shaped bodies, especially in the tissue where necrosis has only partially taken place, in the area showing the hemorrhage. These bodies have exactly the morphology of the typhoid bacillus.

Mesenteric lymph glands show extensive endothelial proliferation.

Intestines show typical typhoid ulcerations.

Liver shows focal necrosis and fatty degeneration; the kidneys parenchymatous degeneration; and the spleen endothelial proliferation.

Bacteriologic Examination. From the abscess of the lung, pleural fluid, left lung, right lung, thrombus in lung, and kidney, B. typhosus was isolated. It was a small, rather slender bacillus, with rounded ends, rather irregular in length, often in threads, which stain fairly well in proportions of 1–2, 1–3, 1–4, 1–6. It was actively motile, did not stain by Gram, gave a positive agglutination with known typhoid serum at 1 : 100 dilution in one hour and grew characteristically in all respects like B. typhosus. Streptococcus pyogenes was isolated from the renal infarct and liver and B. lactis aërogenes from the pulmonary thrombus, kidney, liver, and renal infarction.

Summary. After being in the hospital with a typical attack of typhoid fever twenty-seven days, the patient suddenly develops the

symptoms and signs of lung infarction, after which he passes into a marked toxemic condition and dies eight days later.

At autopsy the main artery leading to the lower lobe of the right lung is found thrombosed, and that lobe is converted almost entirely into an abscess cavity. A bronchopneumonia is found in other portions of the right lung, as well as in the left lung. A pure culture of typhoid bacillus is found in the lung abscess and in both lungs, and bacillus-like bodies alone are seen in sections stained by methylene blue, but no bodies resembling organisms are seen in sections stained by the Gram-Weigert method. In the other organs the lesions are typical of typhoid fever.

As no other causative agent is to be found we feel justified in considering the case one of lung abscess due to B. typhosus, consecutive to pulmonary thrombosis.

A somewhat similar case is reported by Flexner and Harris, in which at autopsy were found typhoid fever without intestinal lesions, typhoid bacteriemia, thrombosis of the main branch of the pulmonary artery supplying the lower lobe of the right lung, gangrene of the lung, perforation of the pleura and pyopneumothorax. The typhoid bacillus was recovered from the consolidated right lung, the spleen, the liver, and the left lung. No other cases of lung abscess or gangrene in typhoid fever with bacteriologic reports have been found in the literature.

From the foregoing cases we feel justified in concluding that B. typhosus is capable of causing pulmonary abscess and gangrene in lung tissue, already the seat of hemorrhagic infarction. That the organism may invade an infarcted area of the lung without causing abscess formation is shown by another case where the pulmonary artery was occluded by a thrombus, typhoid bacilli alone being isolated from the infarcted area. In this case there was no clinical evidence of the infarction. Sections through the pulmonary artery at the site of thrombosis stained with methylene blue showed in several places rod-like bodies lying between the thrombus and the wall of the pulmonary artery. No such bodies could be found in the lungs.

Bronchopneumonia is found quite often in the lungs of patients dying of typhoid fever. When the various inflammatory lesions

produced by the typhoid bacillus are considered it would seem reasonable to suppose that this organism can produce bronchopneumonia. There are, however, but few observations to support this idea.

Chantemesse and Widal, who were the first to investigate the subject, obtained the organism from the lung in two cases and concluded that certain forms of bronchopneumonia, found in typhoid fever, are to be considered as specific manifestations of the disease. Finkler expressed the opinion that B. typhosus causes splenization and bronchopneumonic solidification of similar appearance, without peribronchial solidification and without a tendency to suppuration. Bruneau considers that bronchopneumonia may be caused by a localization of typhoid bacilli in the bronchi or lungs. Lépine and Lyonnet found acute bronchopneumonia in the lungs of a dog killed ten days after injection into the trachea of attenuated cultures of B. typhosus.

Several investigators have isolated the bacillus from bronchopneumonia lungs. Gradwohl found it in pure culture in one case. Bancel, who has made an extensive study of the question of the presence of typhoid bacilli in the lung, concludes that in bronchopneumonia other organisms are usually associated. He isolated by lung puncture B. typhosus and a coccus from a bronchopneumonic lung of a typhoid-fever patient.

In six autopsies upon typhoid-fever cases at the Pennsylvania Hospital, in which cultures were taken from bronchopneumonic areas, the typhoid bacillus was found only once—namely, in the case (Case No. I.) reported here, in which it was obtained in pure culture. As no other organism could be found in a careful microscopic search of the tissues, we consider the bronchopneumonia as caused by the typhoid bacillus. In the other five cases the common pyogenic cocci were isolated.

The role played by the typhoid bacillus in lobar pneumonia, complicating typhoid fever, has been much discussed. The earlier writers (Karlinski, Bruneau and others) considered that lobar pneumonia associated with typhoid fever was always due to a secondary invasion of the pneumococcus. All investigators have found the pneumococcus frequently present in such conditions. It was found

three times in the six cases of lobar pneumonia occurring in typhoid fever patients that have recently come to autopsy at the Pennsylvania Hospital. B. typhosus was isolated in but one case, in which both organisms were obtained. Busquet showed that the typhoid bacillus and pneumococcus can exist together in the circulating blood of patients suffering from pneumonia as a complication of typhoid fever. He obtained both organisms simultaneously by blood culture in two cases.

A similar case has been studied at the Pennsylvania Hospital. A patient entered the hospital on the tenth day of a severe typhoid fever. Three days later his temperature became subnormal and remained so until his death, seven days after his admittance to the ward. No definite signs of pneumonia were noted. On the sixteenth day of his disease 10 c.c. of blood were drawn from his arm vein and distributed among six flasks containing 100 c.c. of broth each, and two flasks containing 100 c.c. of litmus milk each. Smears made from flasks after twenty-four hours at 37° C. showed bacilli, and in all but two flasks, one of milk and one of broth, cocci were seen. By transplanting on human-blood agar the organisms were found to be typical typhoid bacilli, giving a positive serum reaction up to 1:200 dilution in one hour with known typhoid serum, and pneumococci.

In another case of typhoid fever, complicated by lobar pneumonia, B. typhosus was obtained in pure culture from the circulating blood on the seventeenth day of disease, while at autopsy, four days later, the pneumococcus alone was obtained from the heart's blood. Here no doubt the organisms were coexistent in the general circulation during life.

Although there is no doubt that the pneumococcus is the usual cause of lobar pneumonitis in typhoid fever, there is considerable evidence that such a lesion may be caused by the typhoid bacillus. Curschmann expressed the opinion that the typhoid bacillus may cause a true lobar pneumonitis, although this must occur very rarely. One of the earliest workers on this subject, Polguère, expressed a similar belief, while other investigators (Karlinski, Fraenkel, Bruneau, Montier and others) consider a true typhopneumonia as unproved or even impossible.

Mallory describes a case of fibrinous pneumonia occurring during typhoid fever in which many typhoid-bacillus-like bodies and a few pneumococci were found in sections. From his study of the case he considers that the presence of the typhoid toxin may influence by production of epithelioid cells the character of pneumonia produced by the pneumococcus.

A case of pneumonia, lobar in type, recently came to autopsy at the Pennsylvania Hospital; from the lung was cultivated a pure culture of the B. type of the paratyphoid bacillus. We believe from several points of evidence that this organism was the cause of the pneumonia.

Case II.—J. N., Italian laborer aged twenty-one years, entered the service of Dr. Lewis at the Pennsylvania Hospital April 25, 1904 (No. 298). His illness began five days before with fever, chills, and pain in the right side. At time of entrance the patient expectorated bloody sputum. Physical examination showed typical signs of lobar pneumonia. The leukocytes were, however, only 5720. The temperature was somewhat irregular, ranging between 100° and 105°. He died on the eighth day of the disease.

At the autopsy there was found a lobar pneumonitis; acute fibrinous and chronic fibrous pleurisy; acute splenic tumor; cloudy swelling and fatty degeneration of liver; hemorrhages into the gastric mucosa.

The left lung showed no pneumonia, but the right presented an extensive lobar consolidation, crepitus being obtained only along the posterior border. An abstract of the autopsy notes is as follows: Beneath the right pleura small distinct hemorrhages are seen as dark red spots. The cut surface of the right lung is somewhat uneven and has a dark-purple color, through which small bronchioles can be seen. From these bronchioles little masses of yellow purulent material can be expressed. Pinkish-gray streaks of connective tissue are seen running through the cut surface, which appears much like the cut surface of a congested spleen. The lung presents a hemorrhagic appearance.

Sections of the consolidated part of the right lung (Zenker's fluid, paraffin, hematoxylin, and eosin) present the following picture: The alveolar arrangement of the lung can be made out. Throughout the section there are scattered diffusely many polymorphonuclear leuko-

cytes. These, together with fibrin, coagulated material, a few small round cells, and a few desquamated epithelial cells, usually fill the alveoli. The alveolar capillaries are engorged with blood and stand out prominently. In and directly under the pleura, are large collections of red blood corpuscles. In two or three areas masses of red blood cells fill several adjoining alveoli. In other areas many red blood cells are scattered diffusely through the alveoli. In a few places masses of blood appear to replace the lung tissue. The blood-vessels are everywhere filled, and in several of them the blood has a homogeneous conglomerate appearance suggestive of red blood-corpuscle thrombi. There is an amount of yellow and black pigment present.

Sections through the same part of the lung as before described, stained with methylene blue according to the method advised by Flexner for staining typhoid bacilli in the tissues, give the following picture: In a part of the section that contains the largest amount of free blood there are seen blue staining bacillus-like bodies in considerable numbers. These bodies have the morphology of the typhoid bacillus, and are in places arranged in fairly dense masses. Similar sections stained by Gram stain show nothing resembling bacilli, nor is there anything appearing like the pneumococcus to be seen. The fibrin is well stained but in no place does it resemble the bacillus-like bodies described above, being coarser and in longer strands.

Cultures were made on agar plates at time of autopsy from the heart's blood and consolidated area of the right lung, and a tube of human-blood agar was inoculated from the right lung. The plate inoculated from the heart's blood and the blood-agar tube remained sterile after incubation for several days at 37° C. The plate inoculated from the consolidated lung after twenty-four hours' incubation at 37° C. showed three rather dense, round, surface colonies 1 to 3 mm. in diameter, which are distinctly raised and have a dense center and thin edges, where the colonies are semitranslucent. There are about fifteen deep colonies. Coverslips from the surface colonies show somewhat irregular, rather small bacilli. The organism obtained from the lung in pure culture proved to be B. paratyphosus, type B. It was very motile, fermented mannite readily, but did not ferment

lactose or saccharose. It was negative to Gram's stain. Litmus milk was quite blue after four days' incubation at 37° C. The organism gave a positive agglutination reaction with serum from a known case of paratyphoid infection, agglutinating in 1:100 dilution in one hour.

In coverslips from the lung there was seen a few rather long narrow bacilli, and a small number of cocci in pairs resembling the pneumococcus.

Summary. Here is a man dying on the eighth day of a disease in which typical physical signs of pneumonia were found. He had bloody expectoration, and a low leukocyte count. At autopsy there is found a hemorrhagic type of lobar pneumonitis. From the lung tissue a pure culture of the B. type of the paratyphoid bacillus is obtained. No other organisms can be found in the tissues, although smears from the lung show pneumococcus-like organisms.

If this case is, as it seems to be, one of lobar pneumonitis, caused by the paratyphoid bacillus, it would encourage the belief that such a lesion may be produced by another organism of the same group and one so much resembling it in its biology and pathogenicity as B. typhosus.

There are in the literature a number of cases in which the presence of the typhoid bacillus in consolidated lung tissue was proved, while the search did not reveal the pneumococcus. Foà and Bordoni-Uffreduzzi were the first to report a case in which a pure culture of typhoid bacilli was found in inflammatory pulmonary consolidation of lobar extent. They considered it evidence that such a lesion can be produced by other causes than the micrococcus lanceolatus. Anton and Fütterer isolated the bacillus and an undetermined coccus from the lung of a case in which pneumonia developed during typhoid fever. Bruhl reports a case which showed the signs of typhoid fever only after eight days of what seemed a typical attack of pneumonia. The patient was known to have been previously exposed to typhoid infection. B. typhosus was isolated from the lung, and no pneumococci could be found, even by inoculation of mice. The blood of the patient remained sterile. The author considers the case one of a true typhoid bacillus pneumonia. He also quotes a case of Widal in which B. typhosus was isolated by lung puncture from a case

resembling pulmonary tuberculosis. Castaigne reports a similar case, in which lung puncture made two days after the onset of pneumonia showed a pure culture of typhoid bacilli. Inoculation of mice here also failed to show any pneumococci. Finally, Glacer reported a case of frank pneumonia from which a pure culture of typhoid bacilli was obtained by lung puncture and in the lung tissues of which only bacilli could be found

The experimental work upon this subject has been too small to be of much service. Lépine and Lyonnet injected attenuated cultures of typhoid bacilli into the tracheas of eight dogs. Three died very soon after the injection, and enormous hyperemia with hemorrhages were found. One dog was killed ten days after the injection and the lungs showed an acute bronchopneumonia. Four dogs were killed fifteen, seventeen, twenty-four, and thirty days after inoculation, and all showed more or less thickening of the alveolar walls. No true lobar pneumonia was found.

The foregoing cases seem to us to be sufficient to warrant the belief that both the typhoid bacillus and the paratyphoid bacillus, type B, are capable of producing pulmonary inflammation lobar in extent.

The hemorrhagic condition of the pulmonary lesion in our case seems especially worthy of emphasis. The appearance of the lung at time of autopsy was obviously different from that of an ordinary lobar pneumonia. Polguère noticed the hemorrhagic condition of pulmonary lesions of typhoid fever and said that bronchopneumonia in typhoid fever could be produced either by the pneumococcus or by the typhoid bacillus; that caused by the latter being the more hemorrhagic. No other investigator of the subject of typhopneumonia has since mentioned this point.

There is considerable evidence that the pulmonary lesions of typhoid fever are especially hemorrhagic, however, from the condition of the sputum in almost all of the cases reported. Anton and Fütterer appear to have been the first to note that the sputum is hemorrhagic in certain cases of pneumonia occurring during typhoid fever. These authors state that the patient's mouth was full of blood the day after the onset of pneumonia in the sixth day of typhoid fever. Sahli reports a case of typhoid fever which he considers complicated by

pneumonia, rather than lung infarction, in which the sputum was first bloody and then serous. The typhoid bacillus was isolated from the sputum. The sputum is described as hemorrhagic in such cases by Fraenkel, Diendonné, Edel, and Glaser. Stühlern, who isolated the typhoid bacillus twice from the sputum of cases with signs of pulmonary consolidation, describes it in both cases as decidedly hemorrhagic. He considers the bacillus a secondary invader of the lung, and questions whether the hemorrhagic condition of the sputum may not be an effect of the presence of the typhoid bacillus in the lung.

Lépine and Lyonnet, in their experimental work, noted the production of enormous hyperemia with hemorrhages in the lungs following the intratracheal injections of attenuated typhoid bacilli.

The fact that the typhoid bacillus may be present in the lungs in the pulmonary complications of typhoid fever makes it probable that it is not infrequently present also in the sputum under such circumstances. It has been obtained by a number of observers from this source. In 1894 Sahli reported that he obtained the bacillus in pure culture from the sputum. Edel examined the sputum of 11 cases of typhoid fever, 10 of which had bronchitis and 1 had pneumonia. From the case of pneumonia the typhoid bacillus was obtained. The most extensive study of this question has been made by Jehle. He examined the sputum of 15 cases of typhoid fever and found the bacillus in the sputum nine times, twice in pure culture. He also examined the bronchial secretion at autopsy, and isolated the organism twelve times. This includes 5 cases of hemorrhagic infiltration of the lung, all of which showed the presence of the bacilli in the bronchial secretion. The author concludes that the typhoid bacillus is present regularly in the sputum and bronchial secretions in cases of typhoid fever complicated by pneumonic or bronchopneumonic processes, and that it exists there less regularly in the sputum of cases with simple bronchitis only. Diendonné, Glaeer, and recently Rau have reported single cases of pneumonia complicating typhoid fever and showing the organism in the sputum. None were in pure culture.

The organism was recently isolated from the sputum of a case of typhoid fever in the Pennsylvania Hospital.

Case III.—P. B., Italian aged twenty-five years, entered Dr. Scott's service on February 26, 1905, on the tenth day of his disease.

He complained of headache, malaise, and abdominal pain. Rose spots were seen, his spleen was not palpable, and the temperature was 101°. Typhoid bacilli agglutinated by the patient's serum: leukocytes, 5200. On March 10th, the twenty-third day of disease, pain above the liver was complained of. A few fine crepitant rales were heard on inspiration on the right side between the anterior and posterior axillary lines. On the twenty-eighth day of disease there was a well-marked pneumonia over the entire upper part of the right lobe. Leukocytes, 11,100. The next day blood stained sputum was expectorated. On March 18th a blood culture was taken. On the same day cultures of the sputum were made, a technique similar to that of Edel being followed. A fairly large mass of thick tenacious sputum, blood-tinged and deeply rusty throughout, raised by coughing, was collected in a sterile Petri dish and taken directly to the laboratory. The mouth was not previously washed out. In the laboratory the sputum was washed in five successive dishes of sterile salt solution and inoculated on plates of plain agar in two series of three plates each. Plates were also made on glucose agar, in the same dilution as the second in the series. All plates were much overgrown by bacteria except one glucose agar plate, and the third plates of the agar series. From these plates all colonies resembling the typhoid bacillus were transplanted. Only two, one from a glucose agar plate, and one from a plain agar plate, proved to be B. typhosus. The organism is agglutinated by the serum of a known case of typhoid fever in 1: 200 dilution in one hour. From the blood an organism similar in every respect was obtained in pure culture.

The occurrence of the typhoid bacillus in the sputum shows the importance of taking proper means to prevent infection through this source.

Conclusions. The typhoid bacillus not infrequently invades the lung during typhoid fever.

It may invade areas of the lung already the seat of hemorrhagic infarction and there produce abscess formation and gangrene.

The organism may cause bronchopneumonia.

Lobar pneumonia as a complication of typhoid fever is usually due to the pneumococcus. This organism may be present as a general infection in the circulating blood simultaneously with B. typhosus.

It is probable that both B. typhosus and B. paratyphosus, type B, can produce a massive pneumonia, lobar in type. When these organisms are the causative factors the pneumonia is of a peculiar hemorrhagic character, which may be recognized clinically from the bloody nature of the sputum.

The typhoid bacillus is not infrequently found in the sputum of typhoid-fever patients with pulmonary complications. This fact should be emphasized in order that spread of the disease by this means may be prevented.

This work was done under the direction of Dr. W. T. Longcope, and I wish to express my indebtedness to him for much helpful advice.

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Discussion.

Dr. Stengel referred to a second case under his own observation, which, with the one reported by Dr. Robinson, Dr. Stengel had described at the Section on Medicine of the College of Physicians, but had not published. The patient, a physician, came into the German Hospital desperately ill with some thoracic complication of a fever thought to be typhoid, and soon died. Multiple thrombotic lesions were found in the branches of the pulmonary artery, with infarctions that had gone on to complete necrosis. This was so similar to the case that occurred in Dr. Stengel's wards of the Pennsylvania Hospital that the two specimens might have been taken from the same case. Moreover, the clinical symptoms of the first case were so striking, and those in the second case were so like those in the first, that, when the event happened in the second case, Dr. Stengel instantly remembered and spoke of the first case seen twelve years before. As stated, the autopsy showed the same lesions. The symptoms were sudden pulmonary embarrassment, with marked hemorrhagic expectoration. The sputum was almost pure blood, which was sometimes in a state of partial clotting, with disintegration.

Before reporting these cases, Dr. Stengel searched most thoroughly, and found that, with the exception of Dr. Flexner's case, there was on record no certain case of thrombosis of the pulmonary artery in typhoid fever; although a number of systematic writers refer to the possibility of the occurrence of pulmonary (venous?) thrombosis. Thrombus is not so common in the artery as in the veins in typhoid, although it does occur. Dr. Stengel has also been unable to find that thrombus of the pulmonary veins is common in that disease.

As regards causation, there is nothing more than conjecture to furnish a basis for discussion; but he felt that the formation of thrombi is connected with the general toxemia and the bacteremia.

He considered the occurrence in Philadelphia of three cases of a condition, of which he knows of no other satisfactorily recorded instances, as sufficiently noteworthy to be placed on record. His two cases, with one other referred to by Dr. Robinson and that of Flexner and Harris, make four instances of the condition altogether.

April 13, 1905.

Tapeworm from Python Moluris.

By ALLEN J. SMITH, M.D., and Mr. B. F. VEEDER.

Bothridium pythonis, Bienville, 1823; *Bothriocephalus pythonis*, Retzius, 1831; *Tricuspidaria nodulosa*, Mehlis, 1831; *Bothridium laticeps*, Duvernoy, 1833; *Prodicœlia ditrema*, Leblond, 1836; *Solenophorus megalocephalus*, Creplin, 1839; *Bothridium megalocephalum*, Dujardin, 1845; *Dibothrium milliapharyngeus*, Hatch, 1890.

Gross specimens of the parasite and serial sections in different planes of the head and segments were presented before the Society.

The specimens herewith presented, obtained at autopsy from the intestinal tract of a python moluris, recently dead in the Philadelphia Zoological Gardens, were referred to the writers by the pathologist of the Gardens, Dr. C. Y. White, by whose kindness they are now permitted to demonstrate them. While, perhaps, in some measure unsuited for presentation before this Society, the subject is brought forward with reason in that it permits the correction of a mistake which has been published in the Transactions of the Society. On May 22, 1890, and again on April 9, 1891, Dr. J. L. Hatch[1] demonstrated before the Society examples of this same parasite, similarly obtained at autopsy from pythons which had died in the Philadelphia Zoological Gardens; and, regarding his specimens as establishing a new species of tapeworm, proposed for it the name, *Dibothrium milliapharyngeus*. While it is impossible from the meager data published in Hatch's articles to fix the identity of his specimens with these now presented, the recollections of one of the writers, who was familiar with the gross features of Hatch's material, and the identity of derivation, as well as several points of Hatch's description, quite bear out the position assumed. When the present material was first placed in our hands the writers, believing we had to deal with a tapeworm entirely new save for the notices of Hatch, undertook its fuller study with the view of adding to the description preserved in the Transactions of the Society. Close examination, however, soon

[1] Transactions of the Philadelphia Pathological Society, vol. xv. pp. 328 337, and 342.

indicated error on the part of Dr. Hatch and led to the identification of the parasite with a worm first recognized by de Blainville[1] in 1823 under the name *Bothridium pythonis*. Dujardin[2] states that "the genus bothridium was established by Blainville in 1823 for a tapeworm of pythons based upon the structure of the cephalic mass, which instead of having two lateral groove-like suckers, widely open as in bothriocephalus, has two tube-like suckers, formed, as it were, by the partial fusion of the lips of the grooves; although M. de Blainville did not recognize the posterior opening of these cavities." The parasite has perhaps most frequently been spoken of under the name *Solenophorus megalocephalus*, proposed by Creplin[3] in 1830, who, moreover, recognizes a second, larger species, also obtained from pythons, under the name *Soleñophorus grandis*. As far as the writers are aware the only publications referring to the worm from this country are the notices published by Hatch; but it has received considerable attention, especially in connection with its morphology, from French, German, and Italian writers.

Dr. White obtained from the intestinal tract of the dead python several dozen of these tapeworms, for the most part intricately tangled into a large mass and practically without exception broken into fragments of varying length, none more than 25 cm. With this material the writers received five or six heads, each with a few centimeters of the worm attached and several larger fragments, none more than 18 or 20 cm. long and in no case including ripe links.[4]

The full length of the parasite is not represented by any of the portions exhibited, all of which are clearly within the anterior two-

[1] Dujardin, Hist. nat. des Helminthes, Paris, 1845, p. 626. [2] Ibid.

[3] Allg. Encycloped., vol. xxxii. p. 298.

[4] Subsequent search of the remaining material in Dr. White's possession failed to discover ripe links. Moreover, in material kindly furnished from the collection of the Bureau of Animal Industry of the United States Government by Dr. C. W. Stiles, we were unable to meet with egg-bearing segments. However, in a mass of material passed during life from the intestine of a reticulate python in the Philadelphia Zoological Gardens later in the spring of 1905 some 20 cm. or more of fragments of ripe segments of the parasite were obtained, along with over one hundred specimens of *ascaris anoura* and other fragments of the bothridium aggregating more than a meter, including two heads; in these ripe segments the ova were without difficulty obtained. This material has been used in completing the description of the parasite as originally presented to the Society.

thirds of the length, the entire strobile ranging from 25 to 40 cm. or more; the widest links occurring in the latter part of the middle or anterior portion of the last third of the worm. There is considerable variation in width of segments apparently representing proportionate positions in different examples, and the heads in our possession have ranged from 3.5 mm. long and 3.5 mm. wide at widest part to 5 mm. long and 4.5 mm. wide; although as far as the writers are able to make out there is no structural difference to establish the surmise that Creplin's two species are mixed in our material, but suggesting that to a certain extent bulk variation is merely an individual rather than a specific difference. The head is made up of two tubes directed anteroposteriorly, fused together longitudinally and so set that one of the tubes is dorsal and the other ventral to the plane of the neck and strobile. Anteriorly each of the tubular suckers opens by a large linear orifice, directed dorsoventrally, guarded by a pair of large lateral and more or less introverted lips; the posterior opening is inconspicuous and likely to be overlooked except in sections close to the neck segments at the posterior tip of each of the two (dorsal and ventral) halves of the head. In several of our sections it seems to open in a small groove into which may be adapted a fold of tissue, serving to close it in valve-like manner so as to render the organ efficient for its suctorial purposes. Laterally the head is compressed (1 to 1.5 mm.), although wider than the first segments; viewed laterally its outline is that of a truncated oval or ovoid, the truncated end representing the anterior, the rounded the posterior end. When of an ovoid outline the widest dorsoventral diameter is about the posterior third of the head. (From Creplin's description of the large form of solenophorus it is to be supposed that the ovoid form of head particularly belongs to this species; but the variation found in our material bears no relation to the comparative size of the head.) The neck is fused rather closely with the head, the tissue of the former on each lateral face extending forward as a low ridge for a short distance between the tubes. The head is covered with a thin smooth cuticle continuous through both orifices of the tubular suckers with their interior cavities as a simple lining. The walls of the suckers consist largely of a delicate reticular tissue, with a layer of muscle directly beneath the cuticle

and beneath the lining of the cavities. Although carefully sought for, no special cells suggestive of glandular function can be recognized in the wall of the cavities.

In the intertubular tissue in positions corresponding with the borders of the segments are to be seen the beginnings of the lateral (so-called "water-vascular") vessels of the strobile. The segments in the anterior part of the strobile, close to the head, are represented by mere transverse lines; a little further back they become apparent as segments, but are very short and many times wider than long, and have the posterior border well overhanging the anterior part of the succeeding segments; still further back they take on the shape of a long quadrilateral transversely arranged. Gradually as the mature portions of the worm are reached the links elongate and become slightly narrower, until they form short transverse quadrilaterals, or even true squares. The widest segments measure as much as 6 mm. in our material, these evidently coming from near the end of the second third of the strobile; are without ova, and measure from a little less to a little more than a millimeter in length. Ripe segments measure 3.5 to 4 mm. wide and 2 to 3 mm. long, while the terminal ones are probably represented by a few obtained with measurements of 3 to 3.5 mm. wide and 3 mm. long. On the ventral surface in the median line are two openings, the anterior one covered in the non-gravid links by the overhanging posterior border of the preceding link. This orifice, which is provided with rather thick border, is the true genital pore into which open the male and female tubes; the posterior opening being the uterine orifice (tocostome) through which the ova are discharged. Beneath the cuticle and superficial layer of muscle in the parenchyma are scattered numerous testicles, mainly in the lateral fields, communicating by fine canals with the seminal duct. The uterus in the non-gravid links forms a simple coiled tube, but when filled with ova is distended into a somewhat lobulated sac, lying in the median field, with its special orifice on the ventral surface at about the middle of the segment. The ova taken from the uterus are oval in outline, covered with a thin double and flexible wall (often appear more or less wrinkled), the interior being occupied by a plasmatic material in which are numerous larger and smaller yellowish granular cor-

puscles. At each pole the shell membranes are slightly more separated than elsewhere, causing a slight prominence; but no operculum could be detected even after treating the specimens with strong sulphuric acid. Upon marked pressure upon the cover glass, and after treatment with sulphuric acid, the ova commonly ruptured, invariably at one of the poles, but always with a linear tear. The appearance of the internal substance was invariable in the numerous examples of ova examined; it is not due to segmentation, but is evidently made up of vitelline granules. The ova measured ranged from 62 to 66μ in length and from 48 to 54μ in width, averaging 65x50μ. The ovary is bilobed, tubular, and lies back of the uterus in the segments, apparently (but not clearly seen in our material) communicating with the latter by a pavilion.

Discussion.

Dr. Allen J. Smith: This worm, closely related to bothriocephalus, is especially interesting in the suggestion its cephalic structure offers toward the question of the development of the tapeworm head. One might well think of this as a basic form from which the evolution of the grooves of bothriocephalus might proceed by failure of development of the outer part of the wall; nor is it impossible to think of a constriction of each of these tubular cavities near the middle so as to obliterate this part of the tube with preservation of the anterior and posterior orifices, and with such rearrangement in position of these orifices as to produce the common four-cupped type of suckers of tænia and other forms of tapeworm, perhaps the head of such an example as *Mesocestoides lineatus* ranking as an intermediate example. Our ideas as to the derivation of the tapeworm head would fix it as formed from the posterior portion of the embryo and as having analogy with the posterior fixation apparatus of the polystomian trematodes; yet, as a passing question, it might be asked whether such a specimen as this, with its two tube-like suckers, each with an anterior and posterior outlet, could not be thought of as analogous to a double alimentary tube. Some one, Leuckart, I think, has noted cells of glandular appearance in the lining of the suctorial grooves of bothriocephalus latus in the larval stage; and

possibly if one could examine a similar specimen from this worm a like condition might be made out. Such suggestions are, of course, in no sense to be accepted in the present state of our knowledge, but might be found in the future to be not entirely without reason. Were such an idea correct it would suggest a possible origin for the bothriocephalus toxin other than the general tissues of the strobile, namely, as an excretion product from the cephalic cells in the wall of the suctorial grooves.

Epithelioma of the Forehead having its Origin in a Papillary Nevus.

By JAY F. SCHAMBERG, M.D.,

AND

ROSE HIRSCHLER, M.D.

J. C., aged twenty-four years, has had since birth a linear papillary nevus about one and a half inches long extending downward from the hairy border of the forehead to the temporal region. This is characterized by irregular, pale, or slightly yellowish elevations the size of pinheads. In the centre of these prominences are dilated follicular openings. One and a half years ago the patient injured the nevus with an umbrella ferrule and a few months later noticed a growth beginning at this site. This growth has gradually increased in size and others have developed so that at the present time the following appearances are presented: Upon the right side of the forehead occupying the lower portion of a papillary nevus are four split-pea-sized nodules; these are all broken down in the centre and covered with blood crusts. The borders are firm, somewhat pearly in appearance and inclined to be vascular. These have been slowly increasing in size.

Histologic Examination.—Three of the nodules were excised. The pathologic changes found upon microscopic examination are so similar in all the growths as to not require separate description of each.

Under low power there are at once distinguished two distinct circumscribed tumor masses which extend from the subpapillary layer throughout the depth of the corium. These are separated

from each other by a large hair follicle beyond which on both sides is an extensive round-cell infiltration.

The tumor masses are made up of epithelial cells between which a sparse stroma may be seen. The larger of the two masses exhibits an arrangement of the cells in lobuli; the smaller has more of a tubular and acinous appearance. Over the centre of the larger mass in two of the nodules the epidermis is absent, and at this point the epithelial lobuli are separated by wide interstices, some of which contain an edematous stroma with scattered small cells.

The intact portion of the epidermis shows a complete flattening of the papillæ evidently from upward pressure of the growth. The epithelial masses are in these regions separated from the epidermis by but a narrow strip of the corium, which is profusely studded with small cells. The epidermis at the points at which the periphery of the tumor masses slopes away from the epidermis downward into the deeper layers of the corium shows papillæ of normal size. Nowhere are there evident any down-growths of the rete mucosum connecting with the tumor masses. Although a hundred serial sections were prepared and examined no pearly bodies were found.

Some of the sections beyond the tumor border exhibit a great number of sebaceous glands which are so enormous in size as to occupy almost the entire depth of the corium. Some of the glands exhibit not only proliferation of the epithelial cells upon the border of the acini, but also an infiltration of the acini proper. In one area of a sebaceous gland at the extreme end of the section several acini are invaded by a dense and extensive mass of epithelial cells. These acini are surrounded by a fibrous stroma containing numerous round cells and are completely cut off from any epithelial structure. Whether this invasion is the result of an independent carcinomatous proliferation of the mother cells of the gland, or whether it is a secondary involvement from a neighboring structure not shown in the section, cannot be positively stated.

The larger epitheliomatous tumor mass described above appears to have its origin in a budding process of a neighboring hair follicle. This is the follicle which divides the two epitheliomatous tumors.

A lateral off-shoot of the follicle wall extends obliquely downward toward the larger tumor mass.

The epithelial cells of the follicle are not absolutely continuous with those of the tumor, but the hiatus is extremely narrow, and this small intervening space shows irregular groups of epithelial cells. While the origin of this tumor mass is, therefore, not established beyond the peradventure of a doubt, the relation between the follicle wall and the tumor mass is so intimate as to point strongly to origin in the former structure. The intervening stroma between the epithelial masses contains a large number of lymphoid cells, together with abundant plasma cells. *May* 25, 1905.

Interstitial Fibromyoma Complicating Pregnancy.

By R. P. McREYNOLDS.

The specimen was removed by operation from a woman, aged twenty-six years. She conceived for the first time in October, 1904, about a year after marriage, aborted in November, and following this had almost constant hemorrhage until the tumor was removed January 19, 1905. At operation the main tumor was found to be growing toward the uterine cavity and was practically therefore a submucous fibroid, the form which is especially accompanied by endometritis, and often a severe and dangerous hemorrhage.

The point of chief interest in this case was that there was probably a seedling fibroid which delayed conception, and after conception this mass rapidly increased in size, caused abortion, and subsequently constant, severe, and uncontrollable hemorrhage.

Another point of importance is that recent investigations have shown conclusively that the old idea that such tumors never became malignant is erroneous. Dr. Noble's study of 988 cases has shown that sarcoma develped in 1.5 per cent., adenocarcinoma of the corpus uteri in 2.5 per cent., carcinoma of the cervix in 1 per cent., necrosis of the tumor occurred in 6.1 per cent., and cystic degeneration in 3.4 per cent. *January* 26, 1905.

INDEX.

ALBURGER, H. R., anthracosis of liver in pulmonary tuberculosis, 13
tuberculosis vaccinations, 49
Anspach, B. M., pregnancy complicated by fibroid tumor of uterus, 96
Anthracosis of liver in pulmonary tuberculosis, 137

BERGEY, D. H., influence of Pasteurization on the chemical and physical qualities of milk, 102
Blood serum, occurrence of fibrinolytic ferment in, 33
Bone-marrow, study of, typhoid fever and other acute infections, 49
Bovine tubercle bacillus, tabes mesenterica due to, 89

CABINET for teaching disinfection to students, 18
Celluloid strips and sheets for orientation, 108
COCHRAN, C. B., use of food preservatives, 16
COPLIN, W. M. L., cabinet for investigating the action of vaporizable and gaseous disinfectants and insecticides and for teaching disinfection to students, 18
celluloid strips and sheets for the orientation of gross preparations, especially spinal cords, during fixation and handling, and also to facilitate the identification of parts removed for microscopic examination, 108, 109
homogenized cultures of tubercle bacilli, 102
modifications and improvements in the Petri-dish-plate-glass-gelatin method of mounting glass specimens, 93, 95
tabes mesenterica, 93

EPITHELIOMA of forehead having its origin in a papillary nevus, 162
Erosive gastritis, 24
Eshner, A. A., tuberculosis vaccinations, 49
Ewing, James, some aspects of the problem of immunity in typhoid fever, 56

FIBRINOLYTIC ferment in the blood serum, occurrence of, 33
Fibroid tumor of uterus, 96
Fibromyoma, interstitial, complicating pregnancy, 164
Fife, Charles A., tabes mesenterica due to the bovine tubercle bacillus, 89
Food preservatives, use of, 1
Forehead, epithelioma of, 162
Frog, supernumerary anterior extremities in, 22
Funke, John, erosive gastritis, 24
syphilis of liver, 110

GASTRITIS, erosive, 24
Gilliland, S. H., effect of tuberculosis vaccinations upon cattle infected with tuberculosis, 36
Glass specimens, mounting, 93

HARRINGTON, CHARLES, use of food preservatives, 12
Hirschler, R., epithelioma of forehead having its origin in a papillary nevus, 162
Histologic changes encountered in the thymus and elsewhere in a case of congenital hypotonia, 117
Homogenized culture of tubercle bacilli, 97
Hypotonia, congenital, 117

Immunity in typhoid fever, 65
Influence of Pasteurization on the chemical and physical qualities of milk, 102
Interstitial fibromyoma complicating pregnancy, 164
Investigating the action of vaporizable and gaseous disinfectants and insecticides, cabinet for, 18

Liver, anthracosis of, in pulmonary tuberculosis, 137
syphilis of, 110
Loeb, Leo, occurrence of a fibrinolytic ferment in the blood serum, 36
Longcope, Warfield T., study of bone-marrow in typhoid fever and other acute infections, 49
tuberculosis of the thoracic duct and acute miliary tuberculosis, 131

McCarthy, D. J., celluloid strips and sheets for orientation, 108
McConnell, Guthrie, supernumerary anterior extremities in a frog, 22
McFarland, Joseph, occurrence of a fibrinolytic ferment in the blood serum, 33, 36
McReynolds, R. P., interstitial fibromyoma complicating pregnancy, 164
Mesenteric glands, study of, in their relations to tuberculosis, 124
Milk, chemical and physical qualities of, 102
Modifications and improvements in the Petri-dish-plate-glass-gelatin method of mounting glass specimens, 93
Mounting glass specimens, 93

Occurrence of a fibrinolytic ferment in the blood serum, 33
Orientation of gross specimens, celluloid strips and sheets for, 108

Pasteurization, influence of, on the chemical and physical qualities of milk, 102
Pearson, Leonard, effect of tuberculosis vaccinations upon cattle infected with tuberculosis, 36, 49
Pregnancy complicated by fibroid tumor of uterus, 96
interstitial fibromyoma complicating, 166
Python moluris, tapeworm from, 157

Ravenel, M. P., homogenized cultures of tubercle bacilli, 102
mounting glass specimens, 95
tabes mesenterica due to the bovine tubercle bacillus, 89, 93
Robinson, G. C., role of the typhoid bacillus in pulmonary complications of typhoid fever, 141
Rosenberger, R. C., study of homogenized cultures of tubercle bacilli, 97
mesenteric glands in their relations to tuberculosis, 124

Schamberg, J. F., epithelioma of forehead having its origin in a papillary nevus, 162
Smith, A. J., histologic changes encountered in the thymus and elsewhere in a case of congenital hypotonia, 117
tapeworm from python moluris, 157, 161
Stengel, A., pulmonary complications of typhoid fever, 156
Supernumerary anterior extremities in a frog, 22
Syphilis of liver, 110

Tabes mesenterica due to the bovine tubercle bacillus, 89
Tapeworm from python moluris, 157
Thoracic duct, tuberculosis of, 131
Tubercle bacilli, homogenized cultures of, 97
Tuberculosis of thoracic duct and acute miliary tuberculosis, 131
pulmonary, 137
vaccinations, effect of, upon cattle infected with tuberculosis, 36
Typhoid bacillus in pulmonary complications of typhoid fever, 141
fever, bone-marrow in, 49
immunity in, 65
pulmonary complications of, 141

Uterus, fibroid tumor of, 96

Vaccinations, tuberculosis, action of, upon cattle infected with tuberculosis, 36
Vaughan, Victor C., use of food preservatives, 1
Veeder, B. F., tapeworm from python moluris, 157

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